NOV 25 1919

VOLUME 18 NUMBER 6

AMERICAN JOURNAL

OF

DISEASES OF CHILDREN

EDITORIAL BOARD

H. F. HELMHOLZ, Evanston, Ill.

L. EMMETT HOLT, New York City DAVID M. COWIE, Ann Arbor, Mich.

JOHN LOVETT MORSE, Boston EDWIN E. GRAHAM, Philadelphia

JOHN HOWLAND, Baltimore

DECEMBER, 1919

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $4.00

Entered as Second-Class Matter, January 4, 1911, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

JULY, 1919. NUMBER 1.

The Precipitin Reaction in Infant Stools. Ludvig Hektoen, M.D., and Clifford G. Gruleo, M.D., Chicago.

Studies of the Mammary Gland: VI. The Development of the Mammary Gland from Its Earliest Appearance Until the Period of Pregnancy. J. A. Myers, M.S., Ph.D., Minneapolis.

Bacillus Tuberculosis in the Tonsils of Children Clinically Non-Tuberculous. R. S. Austin, M.D., Chicago.

Clothing of Infants in Summer and Winter. L. W. Sauer, M.D., Chicago.

A New Stain for the Diphtheria Bacillus and a Consideration of the Principles Involved in the Staining of this Organism. Roy M. Greenthal, M.D., Ann Arbor, Mich.

The Antiscorbutic Property of Fruits. I. An Experimental Study of Dried Orange Juice. Maurice H. Givens and Harry B. McClugage, Rochester, N. Y.

The Acidotic State of Normal New-Borns with Special Reference to the Alveolar CO_2 Tension, Alkali Tolerance and Acetonuria. Max Seham, M.D., Minneapolis.

Progress in Pediatrics:
Review of Recent Literature on the New-Born. N. O. Pearce, M.D., Minneapolis.

Current Medical Literature.

AUGUST, 1919. NUMBER 2.

A Study of the Relationship of Convulsions in Infancy and Childhood to Epilepsy. John Lovett Morse, M.D., Boston.

Postinfluenzal Encephalitis. Henry Heiman, M.D., New York.

The Constipating Qualities of Orange Juice. H. J. Gerstenberger, M.D., and W. M. Champion, A.B., M.D., Cleveland.

Fat Metabolism of Infants and Young Children. III. Fat in the Stools of Children on a Mixed Diet. L. Emmett Holt, M.D., Angelia M. Courtney and Helen M. Fales, New York.

A Study of the Lactose, Fat and Protein Content of Women's Milk. W. Denis, Ph.D., and Fritz B. Talbot, M.D. (with the assistance of A. S. Minot), Boston.

The Cause of a "Sporadic" Case of Cerebrospinal Meningitis. Henry L. K. Shaw, M.D., Albany, N. Y.

A Classical Case of Hemophilic Arthritis. May G. Wilson, M.D.

Progress in Pediatrics:
Review of Recent Literature on the New-Born. N. O. Pearce, M.D., Minneapolis.

Current Pediatric Literature.

Book Review.

SEPTEMBER, 1919. NUMBER 3.

Leukocyte Counts During Influenza in Infants and Children. J. C. Montgomery, M.D., and E. C. Dunham, M.D., Baltimore.

Fat Metabolism of Infants and Young Children. IV. The Digestion of Some Vegetable Fats by Children on a Mixed Diet. L. Emmett Holt, M.D.; Angelia M. Courtney and Helen L. Fales, New York.

Cerebral Involvement in Hereditary Syphilis. Philip C. Jeans, M.D., St. Louis.

The Incidence and Significance of the Rheumatic Nodules in Children. Joseph Brennemann, M.D., Chicago.

Cerebral Complications in Mumps. Horton R. Casparis, M.D., Baltimore.

A Case of Diabetes Insipidus. David Murray Cowie, M.D., Ann Arbor, Mich.

Observations on the Toxic Properties of Heated and Decomposed Milk and of Milk Cultures of Bacterium Welchii (Bacillus Aerogenes Capsulatus). William W. Ford, M.D., Baltimore.

Progress in Pediatrics:
Review of Recent Literature on the New-Born. N. O. Pearce, M.D., Minneapolis.

Current Pediatric Literature.

OCTOBER, 1919. NUMBER 4.

The Caloric Requirements of Normal Infants and Children from Birth to Puberty. Fritz B. Talbot, M.D., Boston.

Influenzal Croup. Henry Lowndes Lynah, M.D., New York.

A Health Study of a Boy's School. Richard M. Smith, M.D., Boston.

Certain Nutritional Disorders of Children Associated with a Putrefactive Intestinal Flora. Langley Porter, M.D.; G. B. Morris, M.D., and K. F. Meyer, M.D., San Francisco.

Study of the Stools in Children's Institutions Showing the Incidence of Intestinal Parasitic Infections. L. R. DeBuys, B.S., M.D., New Orleans, and H. L. Dwyer, M.D., Kansas City, Mo.

Progress in Pediatrics: Review of Recent Literature on the New-Born. N. O. Pearce, M.D., Minneapolis.

Child Welfare. Report from International Congress.

Current Pediatric Literature.

NOVEMBER, 1919. NUMBER 5.

The Results of Thymus Extirpation in the Dog with a Review of the Experimental Literature on Thymus Extirpation. Edwards A. Park, M.D., and Roy D. McClure, M.D., Baltimore.

Current Pediatric Literature.

COPYRIGHT, 1919, BY THE AMERICAN MEDICAL ASSOCIATION

American Journal of Diseases of Children

Vol. 18 DECEMBER, 1919 No. 6

THE EARLY RECOGNITION OF HYDROCEPHALUS IN MENINGITIS *

KENNETH D. BLACKFAN

BALTIMORE

Interference with absorption of the cerebrospinal fluid in acute meningitis may be brought about by an exudate so localized that it obstructs the foramen of Magendie and the foramina of Luschka, or the exudate may block, partially or completely, the cisternae (magna, interpeduncularis and pontis) at the base of the brain and so prevent the free distribution of cerebrospinal fluid throughout the cerebral subarachnoid space. The spinal subarachnoid space may be filled partially or completely with exudate, thus limiting the participation of this surface in the absorption of the cerebrospinal fluid. Various combinations of these processes may coexist. In any event, if the absorption of cerebrospinal fluid is diminished for a sufficient length of time, hydrocephalus is produced.

A brief discussion of the formation and the circulation of the cerebrospinal fluid and the more recent information concerning hydrocephalus will not be out of place here.

Cerebrospinal fluid is formed within the ventricles from the activity of the choroid plexus. Under normal conditions it passes from the ventricles through the various foramina (foramen of Magendie and foramina of Luschka) to the subarachnoid system where it is absorbed. Absorption in the ventricular system is negligible. From the subarachnoid system the cerebrospinal fluid is absorbed directly into the blood stream. Although absorption takes place from both the cerebral and the spinal subarachnoid systems, cerebral absorption is much greater than spinal absorption. This is due to the fact that the cerebrum offers a much greater absorbing surface and that a more extensive blood vascular area is exposed to contact with the cerebrospinal fluid. Disproportion between the formation and the absorption of cerebrospinal fluid results in its accumulation and its retention within the ventricles.

* From the Harriet Lane Home, Johns Hopkins Hospital, and the Department of Pediatrics, Johns Hopkins University, Baltimore.

Hydrocephalus is secondary to some process that interferes with the normal circulation or absorption of cerebrospinal fluid. Anatomically, two types have been demonstrated: (a) obstructive, and (b) communicating. Obstructive hydrocephalus develops because the cerebrospinal fluid cannot pass from its place of origin in the ventricles to the cerebral and spinal subarachnoid space where absorption takes place. Communicating hydrocephalus — the channels of communication between the ventricles and the spinal subarachnoid space being patent to a greater or less degree — results because the cerebrospinal fluid cannot reach the cerebral subarachnoid space where the greater part of absorption takes place. In the majority of instances this is due to adhesions which obliterate the various cisternae or centers from which the cerebrospinal fluid is distributed over the cortex of the brain. A combination of the two types may result if, in addition to interference with the absorption of the cerebrospinal fluid from the subarachnoid space, there is an inadequate communication between the ventricular and the subarachnoid system.

The primary cause of chronic hydrocephalus in a series of cases studied recently was a previous meningitis in fourteen cases, a congenital absence of the aqueduct of Sylvius in three cases and a tumor blocking the iter in one case.

A differentiation between the two types of hydrocephalus by clinical signs alone is difficult, as the symptoms produced are essentially alike. The type of hydrocephalus may be suggested by the amount of cerebrospinal fluid that is obtained by lumbar puncture. Increase in amount of cerebrospinal fluid in acute infections of the meninges, the influence of posture on the amount of fluid obtained and alteration in the pressure in the cerebrospinal system have to be taken into consideration before drawing conclusions from the results of lumbar puncture alone. The two types of hydrocephalus can be differentiated, however, by the phenolsulphonephthalein test. When phenolsulphonephthalein is injected into the ventricle in obstructive hydrocephalus, the dye does not appear in the cerebrospinal fluid obtained from the lumbar subarachnoid space within forty minutes, if at all. In patients who do not have hydrocephalus and in those with the communicating type of hydrocephalus, the phenolsulphonephthalein appears promptly (in from six to twelve minutes). When phenolsulphonehthalein is injected into the lumbar subarachnoid space in communicating hydrocephalus, absorption of the dye is greatly lessened. Less than 20 per cent. is excreted in the urine within two hours, as compared to 35 or 60 per cent. in normal persons. In obstructive hydrocephalus, when the cisternae and the meninges are not affected, absorption is as prompt as in normal individuals. The phenolsulphonephthalein test

has been employed in the study of a comparatively large number of patients with chronic hydrocephalus, and when carried out properly it affords accurate information regarding the patency of the foramina between the ventricles and the subarachnoid system and the amount of absorption from the subarachnoid space. Recently Dandy[1] suggested that cerebrospinal fluid removed from the ventricle by ventricular puncture be replaced by air. When this is done and a roentgenogram is made, the ventricles appear clearly outlined. By this procedure a hydrocephalus can be demonstrated and its extent measured.

It has long been known that hydrocephalus is a frequent complication of meningitis, but until recently there has been no means by which its early recognition has been possible or a differentiation between the two types of hydrocephalus could be made, both of which are essential for successful treatment.

In the present study I have carried out the phenolsulphonephthalein test[2] in patients with meningitis in which hydrocephalus has developed, and I have had roentgenograms made after the injection of the ventricles with air.[3] Particular attention has been paid to the early diagnosis of hydrocephalus and to the pathologic findings. Twenty-five cases of hydrocephalus were studied.

Meningitis due to the streptococcus, the *Staphylococcus aureus,* the influenza bacillus and the pneumococcus is a terminal manifestation in the majority of instances, secondary to a primary focus elsewhere. The entire course of the meningitis is usually of short duration, which explains the infrequency of hydrocephalus in meningitis due to these organisms. Hydrocephalus was observed, however, in the course of a meningitis due to the influenza bacillus in two patients, 4 and 8 months of age, respectively. They lived about two weeks. A communicating hydrocephalus was demonstrated at necropsy in one patient, and an obstructive hydrocephalus in the other. In the latter, the hydrocephalus was suspected, as it was impossible to obtain more than a few drops of cerebrospinal fluid by lumbar puncture. The phenolsulphonephthalein test showed that an obstruction existed between the ventricular and the subarachnoid systems, and at necropsy the basal foramina were found to be obstructed by a thick purulent exudate.

The infrequency of hydrocephalus in tuberculous meningitis is due, probably, to the relatively slight involvement of the meninges. It is only occasionally that the exudate is so situated or sufficiently

1. Dandy, W. E.: Ann. Surg. **68**:569 (Dec.) 1918. Also: Am. J. Roentgenology **6**:26 (Jan.) 1919; Bull. Johns Hopkins Hosp. **30**:29 (Feb.) 1919.

2. Dandy, W. E., and Blackfan, K. D.: J. Am. Dis. Child. **8**:406 (Nov.) 1914; **14**:424 (Dec.) 1917.

3. I wish to express my thanks to Dr. Walter Dandy and to the staff of the Department of Roentgenology for their assistance in making the roentgenograms.

large in amount to interfere with the avenues of exit of the cerebrospinal fluid from the ventricles or to diminish the absorption from the subarachnoid space by involving the cisternae at the base of the brain. In tuberculous meningitis two cases of communicating hydrocephalus were demonstrated. In each patient phenolsulphonephthalein appeared promptly in the lumbar subarachnoid space after its introduction into the lateral ventricle, but absorption from the subarachnoid space was greatly diminished. At the necropsy the basal foramina were found to be patent, but absorption was limited to the spinal subarachnoid space by an exudate involving the cisternae. In four cases the hydrocephalus was of the obstructive type. In these patients, phenolsulphonephthalein did not appear in the lumbar subarachnoid space after its injection into the ventricles. The foramina of exit at the base of the brain were obliterated by a tuberculous exudate in these cases.

The majority of the cases of hydrocephalus occurred in meningococcus meningitis. Of twenty-five cases occurring in the course of acute meningitis, seventeen were due to the meningococcus. Communicating hydrocephalus developed in eight of the seventeen cases, and in nine the obstructive form was found. Ten of the seventeen patients in this series died and seven recovered. Two of the seven patients had an obstructive hydrocephalus and improvement followed promptly after the introduction of antimeningococcus serum into the ventricles. In four cases in which a communicating hydrocephalus was present, the process became arrested after treatment. The patients made an uneventful recovery. One patient developed a chronic hydrocephalus (communicating). He was 3 months old and was first seen twenty-four hours after the onset of the meningeal symptoms. Meningococci were grown from the blood and the cerebrospinal fluid. Antimeningococcus serum was administered intravenously and into the lumbar subarachnoid space. After the first few days the meningococci disappeared for a time from the cerebrospinal fluid. The temperature remained irregular. The meningeal symptoms did not disappear, and from time to time, in spite of treatment, the organisms would reappear in the cerebrospinal fluid. He was treated intensively with serum introduced into the ventricles and the lumbar subarachnoid space over a period of twenty-four days before the meningococci disappeared permanently and the cerebrospinal fluid became normal. Seven months after the onset of the meningitis, the head was greatly enlarged and a ventriculogram showed almost complete destruction of the cortex (Fig. 1). The patient is alive at the present writing.

A necropsy was performed in the ten fatal cases, and the clinical diagnosis was confirmed by demonstration of the exciting cause of the

hydrocephalus. In seven cases (obstructive hydrocephalus) an exudate occluded the foramina at the base of the brain, and in three cases (communicating hydrocephalus) the basal cisternae were totally obliterated by a thick purulent exudate. Whether an exudate or adhesions are found at necropsy in this form of meningitis depends primarily on the duration of the disease.

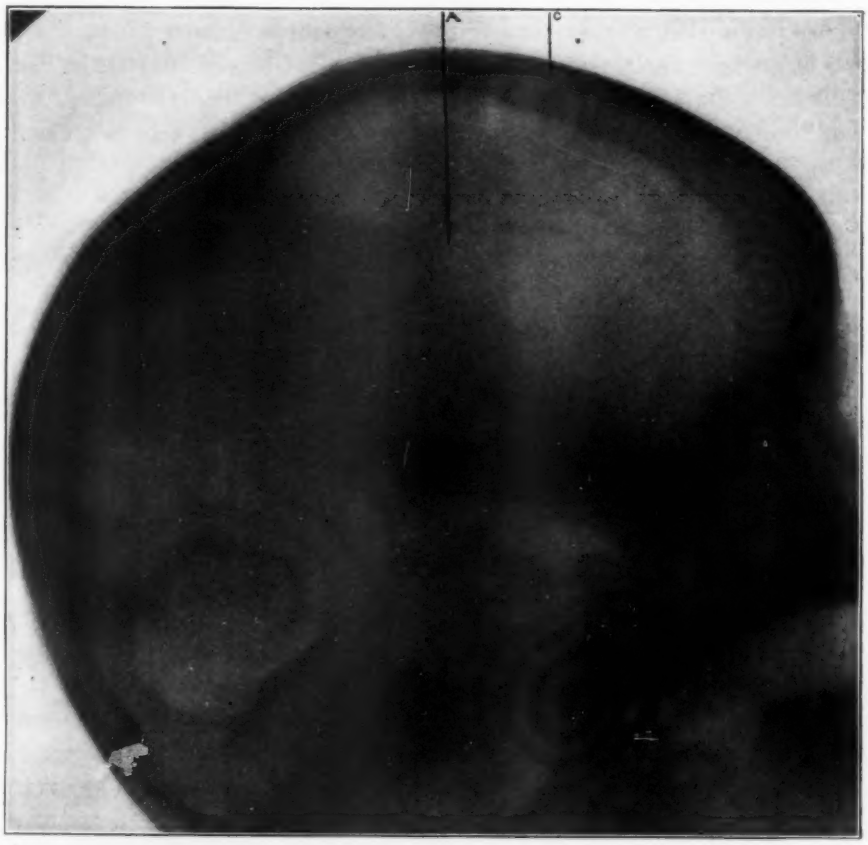

Fig. 1.—Roentgenogram taken seven months after the onset of an acute attack of meningococcus meningitis. The phenolsulphonephthalein test showed that there was a free communication between the ventricles and the spinal subarachnoid space. Absorption from the subarachnoid space was 9 per cent. in two hours. After air injection the roentgenogram showed the lateral ventricles to be markedly dilated (A) and an extreme grade of atrophy of the cortex (C).

It is not within the province of this paper to discuss the pathologic process met with in the various types of meningitis. Acute hydrocephalus in meningitis develops because, as in chronic hydrocephalus, there is a diminution in the absorption of the cerebrospinal fluid. The

important point to recognize is that the lesion must be so located as to obstruct the outflow of cerebrospinal fluid from the ventricles to the subarachnoid space, or else to limit the area of absorption from the spinal or cerebral subarachnoid system. The disappearance of the exudate and the formation of adhesions determine the transition from an acute to a chronic hydrocephalus, and the reestablishment of an equilibrium between the formation of cerebrospinal fluid and its absorption determines whether the process will become arrested or advance progressively. The chronicity of meningococcus meningitis makes it the form of meningitis par excellence for the development of a chronic hydrocephalus. Meningitis due to other organisms almost without exception is fatal, and in a short time.

TABLE 1.—ACUTE HYDROCEPHALUS IN MENINGITIS

Type of Meningitis	No. of Cases of Meningitis with Hydrocephalus Studied	Type of Hydrocephalus	
		Obstructive	Communicating
Influenza bacillus	2	1	1
Tubercle bacillus	6	4	2
Meningococcus	17	9	8
Total	25	14	11

Attention may be directed to a hydrocephalus developing in meningitis by the onset of certain symptoms. The diagnosis is readily established when the condition is of long duration and the symptoms of increased intracranial pressure — headache, stupor, vomiting, enlargement of the head and changes in the eye grounds — are present. The early manifestations of hydrocephalus, however, are so closely interwoven with the symptoms of the meningitis itself, that they are often difficult to recognize. Hydrocephalus should always be suspected with the persistence of symptoms of meningeal irritation (fever, hyperesthesia, irritability or drowsiness, rigidity of the muscles of the neck and extremities, hyperactive reflexes, tremors, etc.) or their reappearance after the symptoms of meningitis have subsided. Infants invariably have a tense and bulging fontanel and in children, Macewen's sign is positive. It should be remembered that these symptoms cannot always be referred to the hydrocephalus alone. We often see at the onset of acute meningitis and throughout the course of the disease manifestations indicative of increased intracranial pressure — headache, fever, vomiting and muscular rigidity — which do not mean necessarily that hydrocephalus is present. I believe that much con-

fusion has been caused by referring to such a condition as hydrocephalus. For instance, in tuberculous meningitis there is present quite constantly a marked increase in the amount of cerebrospinal fluid, but at necropsy a picture quite the reverse of that seen in hydrocephalus is found. The sulci are distended with fluid, the brain is edematous, and though there is a varying increase in the size of the ventricles, one does not find flattening of the convolutions, atrophy and compression of the brain substance and the marked dilatation of the ventricles which characterize the latter condition. A number of patients with tuberculous and meningococcus meningitis who presented such symptoms have been studied by determining the amount of cerebrospinal fluid withdrawn, by the phenolsulphonephthalein test and the pathologic findings at necropsy. In these patients there was no interference with the absorption of cerebrospinal fluid and at necropsy the findings characteristic of hydrocephalus were not present. It is not at all likely that an increase in the amount of cerebrospinal fluid can produce other than a temporary and insignificant hydrocephalus, unless there is an associated diminution in the absorption of the fluid. The results are shown in Table 2.

TABLE 2.—FINDINGS IN CASES OF MENINGITIS WITH INCREASED INTRACRANIAL PRESSURE, BUT NO HYDROCEPHALUS

Case	Diagnosis	Phenolsulphonephthalein Tests		Spinal Fluid		Necropsy
		Patency of Communication, minutes	Absorption from Subarachnoid, per Cent.	Pressure	Amount, C.c.	
1	Tuberculous meningitis	10	45	Increased	40	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae
2	Tuberculous meningitis	12	40	Increased	55	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae
3	Tuberculous meningitis	8	38	Increased	35	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae
4	Tuberculous meningitis	14	42	Increased	45	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae
5	Meningococcus meningitis	12	55	Increased	60	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae
6	Meningococcus meningitis	10	48	Increased	40	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae
7	Meningococcus meningitis	8	62	Increased	45	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae

Abnormal changes in the eye grounds and enlargement of the head, when present, are symptoms indicative of an hydrocephalus, but they are seldom seen early in its development and so are of but little aid in making the diagnosis. This is especially true before the fontanels are closed and the sutures are firmly united. A considerable atrophy and compression of the brain takes place before the intraventricular pressure becomes sufficient to cause marked changes in the eye grounds and an enlargement of the head. This is well illustrated in the case of an infant, 3 months of age, who was observed from the onset of an acute meningococcus meningitis throughout the various stages of development from an acute to a chronic hydrocephalus. This is graphically shown in Table 3.

TABLE 3.—FINDINGS IN A CASE OF ACUTE MENINGOCOCCUS MENINGITIS DEVELOPING FROM AN ACUTE TO A CHRONIC HYDROCEPHALUS

Duration of Disease	Circumference of Head	Eye Grounds	Roentgenogram of Ventricles	Phenolsulphonephthalein Tests		Symptoms
				Patency of Communication	Absorption from Subarachnoid Space	
Onset	44 cm.	.....	.....	....	...	Collapse, fever, depressed fontanel, petechiae
1 mo.	44 cm.	Normal	.....	....	...	Bulging fontanel, rigidity, hyperesthesia
2 mo.	44 cm.	.....	.....	....	....	Bulging fontanels, rigidity, opisthotonus
3 mo.	44.3 cm.	Slight dilatation of retinal vessels. Margin of disk clear. Normal physiologic cupping	Ventricles dilated. Marked cortical atrophy	+	9%	Bulging fontanels, rigidity, opisthotonus
4 mo.	46.5 cm.	Same	Same	+	9%	Opisthotonus disappeared, vomiting, tense fontanels
7 mo.	49.5 cm.	Same	Practically no cortex seen. Ventricles greatly enlarged	....	....	Bulging fontanels, separation of sutures, craniotabes, rigidity, vomiting, emaciation

The amount of cerebrospinal fluid obtained by lumbar puncture affords the most helpful clinical sign of hydrocephalus, although, as previously mentioned, it is not absolutely dependable. In hydrocephalus the cerebrospinal fluid is under greatly increased pressure and an abnormal amount is obtained readily or it is obtained in small amount and with difficulty.

A definite increase in the amount of cerebrospinal fluid of 50 c.c. or more, withdrawn repeatedly when the other signs of the acute infection of the meninges have subsided, is significant of a communi-

cating hydrocephalus. While this is suggestive evidence, it is not sufficient in itself to establish the diagnosis, as relatively large amounts of cerebrospinal fluid are sometimes found in obstructive hydrocephalus.

Small amounts of cerebrospinal fluid obtained by lumbar puncture suggest an obstructive hydrocephalus. If the subarachnoid space has been entered, and the fluid is not too thick to run through the needle, it is relatively safe to conclude that there is an exudate so situated as to prevent the free flow of cerebrospinal fluid from the ventricles to the spinal subarachnoid space. In obstructive hydrocephalus relatively large amounts of cerebrospinal fluid may be recovered at the first

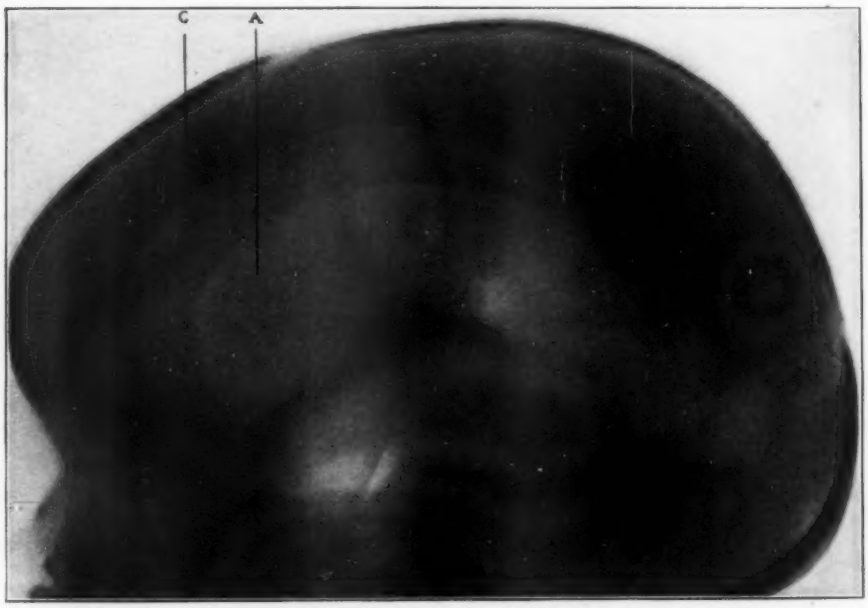

Fig. 2.—Obstructive hydrocephalus in a patient aged 3 months. The onset of the hydrocephalus was suggested by the persistence of the symptoms of meningitis. The cerebrospinal fluid was obtained readily for ten days and then only a few drops flowed from the needle. The phenolsulphonephthalein test showed that there was no communication between the ventricles and the subarachnoid space. Absorption from the subarachnoid space was 55 per cent. in two hours. After air injection the roentgenogram showed dilated lateral ventricle (A) with atrophy of the cortex (C).

lumbar puncture and then the quantity lessens so that only a few drops are obtained at successive punctures (Fig. 2). Corroborative evidence of the presence of hydrocephalus may be shown by the results from puncture of the ventricle, as in such cases the cerebrospinal fluid in the ventricles is under increased pressure and an excessive amount can be withdrawn.

The early recognition of hydrocephalus is of practical importance in meningitis due to the meningococcus. Many cases of hydrocephalus, the result of meningococcus meningitis, are reported in the literature in which the hydrocephalus developed despite treatment with antimeningococcus serum. In the majority of instances this has occurred when treatment was instituted late, for the outcome at this stage of the disease, even with appropriate treatment, is uncertain (Fig. 3). The earlier and the more intensive the treatment, the better the chance of recovery. In obstructive hydrocephalus if the serum is introduced

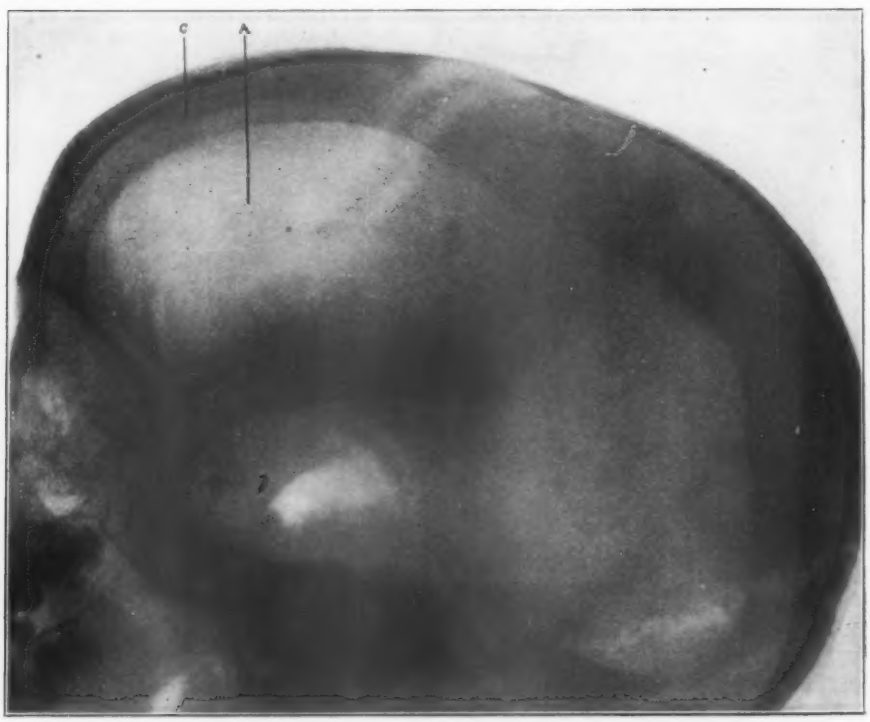

Fig. 3.—Communicating hydrocephalus in a patient, 2 years old, who was untreated for six weeks following the onset of an acute meningococcus meningitis. Examination showed rigidity of the neck, positive Kernig's sign and a low grade optic neuritis. The phenolsulphonephthalein test showed that there was a free communication between the ventricles and the subarachnoid space. Absorption from the subarachnoid space was 8 per cent. in two hours. After air injection the roentgenogram showed dilated ventricles (A) with atrophy and compression of the cerebral cortex (C). The patient died in spite of the administration of antimeningococcus serum into the ventricles and into the lumbar subarachnoid space.

only by lumbar subarachnoid injection there is the danger of organization of the exudate and also that the meningococci remaining in the

ventricles are not subjected to the influence of the serum. In this form of hydrocephalus the antimeningococcus serum should be injected directly into the ventricle as well as into the lumbar subarachnoid space. In communicating hydrocephalus intraventricular injection of serum also is advisable. A larger amount may be injected and thereby brought into direct contact with the exudate and in greater concentration than by the lumbar subarachnoid injection alone. (Fig. 4).

The capacity of the meninges to absorb cerebrospinal fluid should be tested by the lumbar subarachnoid injection of phenolsulphonephthalein, when the symptoms of meningeal irritation persist or when

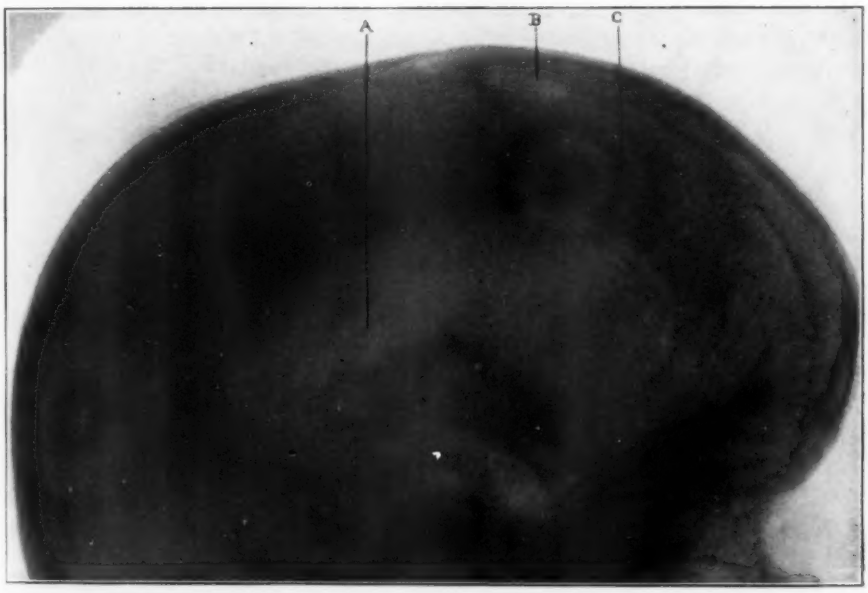

Fig. 4.—The patient, aged 3 years, was treated for two weeks with antimeningococcus serum. He did not improve and meningococci persisted in the cerebrospinal fluid. The phenolsulphonephthalein test showed that absorption from the subarachnoid space was diminished (13 per cent. in two hours). Ventricular injection of the dye through a trephine opening demonstrated a communication between the ventricles and the lumbar subarachnoid space. After air injection the roentgenogram shows enlarged lateral ventricles (A), the trephine opening (B) and compression and atrophy of the cerebral cortex (C). After three injections of antimeningococcus serum into the ventricles, the organisms disappeared. The patient made an uneventful recovery.

they reappear after the vigorous use of antimeningococcus serum. A distinct diminution in the absorption of cerebrospinal fluid indicates a communicating hydrocephalus. This diagnosis can be confirmed by determining the patency of the foramina between the ventricular and

the subarachnoid systems by the injection of phenolsulphonephthalein directly into the ventricle. If the symptoms are the result of an obstructive hydrocephalus the absorption of the cerebrospinal fluid from the lumbar subarachnoid space will not be diminished. The diagnosis in this type of hydrocephalus will then depend on the non-appearance of phenolsulphonephthalein in the lumbar subarachnoid space after its injection into the ventricle. These tests add nothing to the severity of the treatment. They do not demand any unnecessary operative procedure, as under such circumstances it is necessary to bring serum, either through an open fontanel or through a trephine opening, in so large an amount and in as concentrated a form as possible, directly in contact with the purulent exudate at the base of the brain.

STAMMERING AS A DISORDER OF SPEECH DEPENDENT ON CONDITIONS OF CHILD DEVELOPMENT *

ELMER L. KENYON, M.D.

CHICAGO

As the facts concerned with child development become collaborated into a more exact and unified body of scientific knowledge, it will become easier to understand tendencies to perversion from the normal that may appear at any point in the child's developmental progress. The ultimate attainment of normality in the adult depends on two great factors: (1) Hereditary and congenital anatomic and physiologic foundations; and the persistence of the normality of these congenital foundations during the period of (2) the physiologic processes of development. The foundations concern matters of physical structure and organization of all organs, including brain and nervous system, and concern the sexual organization, whether male or female. But also the physiologic processes of development must take hold of these anatomic and physiologic foundations and modify and advance them safely to final matured conditions and processes according to developmental laws.

In the course of this upward road, however, lie many possibilities for accident and physiologic perversion, which gradually become less and less menacing as the point of developmental maturity is approached. During the developmental period of the child, nothing, mental or physical, is in its final state. The anatomic and physiologic factors are on their way, and, being subject to the laws of development, are also capable of becoming misdirected by forces which disturb the operation of these developmental laws. We know what the child is, but we do not know certainly what he may become at any moment. The dangers of this developmental period may be summarized as involving: (1) Conditions of nutrition; (2) conditions of disease; (3) physical accident; (4) conditions of environment, and (5) conditions of management of the child.

Congenital and developmental speech disorders are concerned with (1) anatomic and physiologic foundations and (2) with developmental perversions. The closer we keep our minds on these scientific realms of congenital foundations and child development, and their peculiar problems, the more exact will become our understanding of congenital

---

* Presented by invitation to the National Society for the Study and Correction of Speech Disorder, at Milwaukee, July 4, 1919.

and developmental speech disorders. We are accustomed to look on the defects of articulation in children as congenital or developmental problems, but we are not accustomed to classify stammering so definitely in this category. And yet in probably more than 95 per cent. of the cases, stammering is initiated during the speech development period, and in probably more than 99 per cent. of the cases it is initiated before the twentieth year. The disorder is, therefore, clearly involved at its origin in the developmental processes of childhood, even as the articulative disorders are so involved, and should be classified frankly with them as a developmental disorder of speech.

This evident dependence of stammering on congenital and developmental conditions must be reckoned with if the cause of stammering is to be understood. Dominated by a certain superficiality in our realization of the processes of physiologic development in the child, we have habituated ourselves to include in our view of speech development only the acquirement of the elemental sounds, words and sentences, in connection with the mental processes behind the attainment of these physical results. We have quite overlooked another process and necessity of speech development, a process which, although concrete and real, is, nevertheless, so subtle as to furnish its own explanation for this oversight. These beginning acts of speech must be exercised while the child is acquiring its first impressions of the great world, and especially while it is learning to associate with other people, and to think and talk under conditions of social interrelations. Here, then, lies an overlooked factor in the development of speech, a factor obviously capable of producing perversion, namely, the psychologic influence on the childish mind of social interrelations during the period of the development of the mind, and during the development of speech. No child can avoid the necessity of mastering the problems of speech development under whatever difficulties may be engendered by the social contacts of childhood. If we are to understand stammering, it is necessary to approach the initiation of the disorder from the standpoint of this newly realized factor in speech development. In order to make the importance of this conception understood it will be necessary to discuss not only certain aspects of the psychology of social intercourse in general, but also certain innate difficulties which the child experiences while learning to talk.

CONCERNING THE PSYCHOLOGY OF SOCIAL INTERRELATIONS

One of the most profound and important truths concerning the human being has reference to the psychical manifestations incited by social interrelations. One needs only to recall such phenomena as those of "suggestion," of "mob psychology," of social emotionalism and even of hypnotism, to realize the importance of social interrela-

tions on the human mind and body. The human personality seems to be conceived and organized in large part to influence other personalities and to be influenced by them. The human ego is vulnerable socially in variable degrees. All persons are played on by social interrelations to some degree mentally. Some are highly, even pathologically, impressionable. The highly susceptible individual is under certain social circumstances thrown into a serious status of emotion, which profoundly disturbs his ease, his clearness of mind, his capability of concentration, exercise of will, naturalness of manner, memory, indeed, all phases of his mental activity. Degrees of susceptibility vary with individuals, and degrees of intensity of manifestation vary in the same individual.

The profundity of this form of manifestation of emotional disturbance is not generally understood. We pass it off lightly as a manifestation of emotional states so common as to be hardly worthy of analyzation, and we designate it as "embarrassment," "diffidence," "shyness," or "stage fright," and the like. Only the highly susceptible realize keenly the profound importance of this phenomenon. Only the deeper sufferers can know how seriously the ordinary social and business interrelations of life are affected. Only they can know the innate strugglings and sufferings and trials and handicaps caused by their own extreme susceptibility to this emotional disturbance. In the more marked manifestations of susceptibility to social emotion one cannot avoid realizing a certain resemblance to hypnotism.

The manifestations of the emotion engendered by social intercourse are not alone mental. They involve commonly also such physical disturbances as clumsiness of physical movement, trembling of the hands, difficulty of management of the legs in walking, a pseudoparesis of muscles of the lips while talking, or of the chest, increased muscular tension, either general or local, and other physical manifestations.

SOCIAL EMOTION IN CHILDHOOD

This phenomenon takes root in childhood, extending backward to a point at any rate preceding the end of the third year of life, or, rather, it has already found its root in the very nature of the child itself. We may presume that fears of a vague sort precede the awakening of the childish mind to this more subtle and more intellectual form of mental impressionability. The child during the early years of the speech development period is peculiarly the emotionally apprehensive victim of its own lack of understanding and of reasoning. All is mystery and wonder, and mystery is the creator of fears. The child lives in a world of apprehension, because fact and reasoning are not present to straighten out the understanding of the strange world and its mysteries. The personalities met with are

awesome and fear inciting to a degree not comprehensible to the adult, unless the mental conditions of childhood are weighed. Thus circumstances quite incapable of affecting the adult may cast the child into paroxysms of apprehension.

And with all this susceptibility to emotional disturbance there is present a corresponding impulsiveness of conduct, because the foundations of inhibitive selfcontrol are as yet scarcely laid. For self-control depends on the understanding of the facts of life and on a certain capability of reasoning that points out the need for the exercise of self-control under given circumstances. These inhibitive activities begin early, to be sure, even with the beginnings of thought, but their progress of development is even as slow and patient as the developmental processes of the mind generally.

PHYSICAL, MENTAL AND SPEECH CONDITIONS OF EARLY CHILDHOOD

Moreover and more specifically, the psychoneuromuscular acts of speech in the young child are always in a greater or less state of uncertainty. In the first place, the peripheral organs of speech are but crudely trained for their highly delicate and highly difficult operations. Back of this unresponsive state of the peripheral organs of speech are, likewise, crudely educated memories of sounds and words, both in the receptive (sensory) word center and in the outgoing (motor) word center. The mental conceptions, then, both of the words to be expressed and of the muscular movements required for their expression, are vague and confused. Moreover, the processes of thought building and of sentence building are likewise simple and uncertain. All of this is quite normal to the developing child. Given normal physiologic foundations and the development of speech may usually be expected to proceed normally.

But enlightenment begins to dawn regarding causes for the incitation to stammering, when we have put all these facts together and have noted how frail a human mental structure and how uncertain a speech structure, and, consequently, how readily susceptible to perversion these developmental processes of speech are. The child must enter into his understanding of the world and into his own self-management in the great game of social intercourse not only handicapped by his own impulsive, precipitate, unreasoning, impressionable, apprehensive nature, but also handicapped by the childish psychophysical uncertainty, in both the mental and physical realms of speech; and, moreover, possessed of a natural more or less active susceptibility to emotional perturbation. He enters this game with certain congenital foundations, more or less perfect or imperfect, with conditions of temperamental excitability and of emotionalism varying within normal or abnormal limits, with a hold on the speech processes more or less

insecure, with the conditions of health and of environment and of guidance more or less favorable or unfavorable. Whether he shall master the difficulties of this developmental game, or whether he shall take the false step that leads to stammering, is dependent on conditions which it shall be our further effort to understand.

The child may face the problem of social and speech development with peculiar handicaps, as we have already indicated. He may have been granted congenitally a nervous organization more than ordinarily susceptible to excitation, or he may have been granted a congenital tendency to overrapidity of speech, or an unusual susceptibility to emotional excitement; or he may have been born with a frailty of physical and nervous organization. He may be handicapped at some point in his developmental career by disease or injury, and possibly by a slow period of convalescence. Such disturbances are prone to produce marked effects on the physiologic processes, and especially on the developmental physiologic processes of the brain and nervous system, and on conditions affecting nervous excitability and emotionalism.

The environment of the child may tend to augment the difficulties of general development and of speech development. For example, a large family may serve to add to the nervous stress of a developing child; likewise, a nervous parent, or one who is overbearing, or a domineering older brother, may have a serious determining influence. The strenuousness, or nervousness, of the social or industrial life in certain families may react strongly and adversely on the nervous tendencies of the child. Persistently wrong habits of eating, or sleeping, or of overwork, mental or physical, or other sorts of misguidance may be determining factors in disturbing the processes of normal speech development.

THE NATURE OF STAMMERING

We have thus attempted to present a groundwork of developmental conditions related to childhood on which the disturbance of speech that we call stammering rests. In my opinion stammering results when states of mental and emotional stress, founded on congenital and developmental conditions and incited by social interrelations, become in the particular child disproportionate to his childish ability to maintain normal self-control. In order to make this view clearer, let us ask ourselves the question, "What is stammering?" Stammering consists, on the one hand, of a perversion of the action of the muscles of speech during speech production, and, on the other hand, of an intimately associated mental disturbance, more or less severe. One striking fact concerning the disorder is its irregularity of manifestation, and especially the dependence of its manifestations on the conditions of social intercourse present at the moment. And

a second striking fact is the identity of the emotional states of the stammerer with such states in the nonstammerer when emotionally disturbed by social relations. In other words, the individual who is susceptible to stammering stammers only when emotionally disturbed in a certain way by social circumstances, exactly as a nonstammerer is emotionally disturbed by similar circumstances, but without stammering. If the susceptible individual stammers when not in a state of emotion, as for example, when talking by himself alone (a rare occurrence), his stammering is reduced to a mere pittance of its usual character, and is due to habit alone, or else it is incited by active memories of past emotional disturbances. If he talks with people and feels little or no emotion he does not stammer.

Within the past few years attempts have been made to find the cause of stammering in certain specific disturbances of normal mental phenomena, especially by Dr. C. S. Bluemel.[1] But it is to be noted that such mental disturbance cannot be explanatory of stammering in a complete sense, unless the relation of these phenomena to the muscular disturbances in the peripheral organs of speech be explained. The mere lapse of memory for a sound, or a word, is as incapable in itself of producing muscular spasm as is the lapse of memory for proper names which is so commonly manifested. Lapse of memory is not stammering and of itself alone is obviously incapable of producing stammering. If such lapse of memory results in stammering, it is because of other allied causative factors. And it is these factors which I hope we may now come to understand.

The child, disturbed by emotional excitement engendered by its social situation, not sure of himself either as to his general mental condition, or the thought to be expressed, or the words to be employed, hampered possibly by emotionally perturbed organs of speech, or by their clumsiness of action, and yet impelled by his own impulsive nature, as well as by his emotional excitement, to plunge on with the talking, is thus precipitated into *speech stampede*. For the moment, the normal guidance of the peripheral speech machine is lacking. The engine, which is already under headway, at least on the mental side, has got out of control. Nervous and muscular overaction thus come to be overapplied at certain points for a moment, or longer, and thereby the action of the entire machine is for that period of time hampered. Partial recovery of mental poise reacts to encourage normal redirection of the machine. The action hitches or moves more smoothly according to the degree of emotional excitement present; always, however, with a tendency to the ease of action present under nonemotional conditions.

1. Bluemel, C. S.: Stammering and Cognate Defects of Speech, 1913, 2 vols., N. Y., G. E. Stechert & Co.

The elements essential to this speech panic are (1) emotional excitement; (2) mental confusion with especial reference to the speech, and (3) the seemingly (childish) imperative necessity of going on with the talking (that is, without the exercise of inhibitive control). The rushing on with the talking without first becoming self-controlled is dependent on the impulsive nature of the child and on the emotional excitement at the moment; and also the mental confusion is dependent, at any rate in large part, on the emotional excitement. Emotional perturbation is, then, the great fundamental cause of the spasmodic disturbance of speech.[2]

But in the background of this picture of the essential elements required to initiate stammering, lie all the congenital, nutritional, physically pathologic, and environmental, circumstances of which I have heretofore spoken, that tend to aggravate the emotional uncontrollability of the child. And, moreover, lying also in the background, are other possible circumstances serving as aggravating causes; for example, association with another stammerer, or Dr. Bluemel's failure on the part of the memory processes of the auditory word center, or Dr. Walter B. Swift's disturbance in the visualization processes.[3] Both these latter phenomena are, however, in my opinion, secondary and dependent on the status of emotion present.

An interesting and instructive fact in this connection is the overwhelming preponderance of the children who pass through the "psychical contagion" of association with a stammerer harmlessly. Behind such association, if stammering is to result, must lie other factors, either pervasive and necessary, or else accidental. Elements essential to produce a speech stampede must be present. These have to do, I believe, with undue emotional excitement. One other possible exciting factor must also not be overlooked. That is, the embarrassing disturbance of sensation, or of readiness of movement, due to emotion, sometimes present in the peripheral organs and active in many emotional nonstammerers. In stammerers such pseudoparetic factors may be present either in the chest or in the articulative organs, especially in the lips and tongue.

It is also to be noted that the child who experiences the state of emotional excitement described is thereby rendered highly conscious of its own embarrassing situation. This self-consciousness leads eventually almost inevitably to pseudoconscious muscular efforts applied

---

2. The very beginnings of stammering commonly consist of light repetitions of the first sound of words, produced under usually evident conditions of slight emotional excitement. The more intense manifestations in such cases are matters of gradual development.

3. Swift, W. B.: A Psychological Analysis of Stammering, J. Abnorm. Psychol. **10**:225 (Oct.-Nov.) 1915.

to the peripheral speech organs. Since the child has no knowledge of how to operate its speech machine consciously, and since this conscious struggle necessarily interferes with the normal subconscious action of the directing motor word center, such pseudoconscious efforts at speech production must almost certainly be directed wrongly. This tends to complicate the speech confusion. Under the psychologic confusions of the situation the only conscious efforts that would tend to relieve the situation would be those directed toward temporary inhibition of speech, and to self-control. Such pseudoconscious wrong efforts in the production of speech are so evident in some young stammerers that one is led to wonder whether emotional excitement coupled with these efforts are not of themselves alone capable of inciting serious stammering.[4]

DEVELOPMENTAL GROWTH OF INTENSITY OF THE STAMMERING

Once the tendency for the emotionally perturbed speech machine to go wrong has been initiated, the continuation of such misdirection, under similar mental conditions and in the absence of inhibitive self-control, is well nigh inevitable, because the fixed processes of speech are as yet not established. The establishment of habits, being an important element of the developmental processes of childhood in general, readily and naturally applies itself to the entire abnormal process of stammering, both mental and physical. The repetition of this spasmodic perversion of the acts of speech is of itself, producing as it does increased embarrassment, a cause for increased emotionalism and excitability. Susceptibility to emotionalism and excitability undergoes a gradual developmental increase, until it often becomes extreme and even pathologic. Then, also, through the persistent increase of nervous stress in the child's social life the development of the entire character is modified. The stammerer tends to develop into a being intensely perturbed by the fear of social contacts; his fear causes him to avoid social relations, he suffers much mentally, he remains apart from others and thus loses the character building benefits of free social intercourse. The mental disturbances of stammering become important intrinsic factors in all the mental developmental processes, and, as if an active, disturbing evil influence had lodged itself in the mind of the child, the entire character building processes are involved about the machinations of this intrinsic, trouble breeding, thing of evil. The mature stammerer thus becomes the unfortunate victim of perversions of development, causing him to be mentally, nervously and emotionally to an important degree a different being from that

4. Mr. Ernest Tompkins considers stammering to be "a conscious effort at speech clashing with the normal speech," Pedagogical Seminary, June, 1915.

he would have been had he not stammered. And a fundamental seriousness of the disorder is due to the fact that the sufferer is not merely a person who stammers, but is, rather, a stammering person. And here lies the great difficulty experienced in eradicating stammering, and the equally great need of treatment early, at the very moment of its incitation, if possible.

SUMMARY AND CONCLUSIONS

Stammering in most cases begins in early childhood, and should be considered as a perversion of the normal processes of speech development. This perversion of the normal speech processes is dependent on emotional disturbance arising from the necessity of developing the speech function under the trying conditions of social interrelations. Thus there are aroused in the child more or less profound manifestations of "social emotion." Behind this exciting cause often lie congenital foundations and environmental conditions, which tend to encourage the natural childish tendencies to excitability and emotionalism. Natural childish characteristics—impulsiveness, lack of self-control, relative absence of knowledge and reasoning, apprehensiveness —as well as the doubtful, wavering, clumsy, state of partial development of the speech function, both constitute factors which help to render the child susceptible to this manner of speech perversion.

The immediate psychology of the incitation to stammering involves (1) emotional excitement; (2) mental confusion, and (3) the impulsive effort to talk while in this uncertain state of mind. The result is a speech panic, in which normal control of the peripheral speech machine is for the moment lost. In the background of this immediate mental picture lie various disturbing phenomena which add to the mental confusion.

These beginning perversions of the speech act are often repeated; the mental stress behind them becomes a more or less constant status of mind. These mental and physical perversions play a baneful part in the general mental and physical physiologic processes of development. Thus the susceptibility to emotionalism and excitability slowly increase, both as to uncontrollableness and to intensity; and likewise the physical manifestations in the peripheral organs of speech.

And all of this cannot go on for months and years without having its influence in perverting the development of the character in general. The advanced stammerer has become a stammering person, rather than an entirely normal person who stammers. This fact renders the complete eradication of the disorder exceedingly difficult, and calls for the beginning of treatment at the earliest possible time, preferably at the very beginning of the manifestations.

104 South Michigan Boulevard.

THE RÔLE OF THE ANTINEURITIC VITAMIN IN THE ARTIFICIAL FEEDING OF INFANTS*

AMY L. DANIELS, PH.D., AND ALBERT H. BYFIELD, M.D.
WITH THE COOPERATION OF
ROSEMARY LOUGHLIN, M.S.
IOWA CITY, IOWA

From time immemorial substitutes for human milk have been sought in the mammary secretions of other animals. The inadequacy of such substitutes has been made apparent by the distinctly higher incidence of disease and death among artificially fed babies. Early attempts were directed toward the correction of the grosser difficulties. By variously modifying and diluting the substituted milks—more particularly cow's milk—these have been rendered more acceptable to the digestion and quantitative needs of the infant. As a result, artificial feeding in the hands of the skilful worker has been fairly successful if measured in terms of disease and death. But so concerned have we been with the more obvious disturbances that little attention has been paid to the possible deficiencies of these diluted milks which may render them greatly inferior to human milk as far as their growth promoting factors are concerned, although experience has taught that the addition of other substances to the milk diet has been found to be not only desirable but necessary as early as the sixth month.

While students of nutrition have for some time been awake to the importance of the antineuritic vitamin as an essential factor in growth and physiologic well being, with the exception of cases of beriberi, there has been little consideration of a possible relationship between this growth factor and nutritional disturbances in infancy. The reason for this is possibly due to the fact that a paucity of this material produces such subtle changes that the interest of the pediatrician has not been drawn to them, especially since until very recently we have believed milk to be a valuable source of this food accessory.

That milk is comparatively low in the antineuritic vitamin has been pointed out by both Gibson and Concepcion[1] and Osborne and Mendel.[2] The former investigators, working with dogs and pigs

* From the Department of Nutrition, Iowa Child Welfare Research Station and the Department of Pediatrics, State University of Iowa.

1. Gibson, R. B., and Concepcion, I.: Philippine J. Sc. B. **11**:119 (May) 1916.
2. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **34**:537 (June) 1918.

on problems pertaining to infantile beriberi, found that the addition of milk to diets consisting largely of polished rice did not protect against symptoms of polyneuritis, a disease which is known to be caused by a lack of this food accessory; while Osborne and Mendel demonstrated its low concentration through feeding experiments with rats, where milk was the sole source of the vitamin. Both groups of investigators have suggested that some of the difficulties in artificially fed babies may be due to an insufficient amount of the vitamin material. Indeed, Gibson and Concepcion believe that even in breast fed babies the diet should be extended as soon as possible. These state that "The young of healthy mothers probably come into the world with a reserve supply of the vitamin substances sufficient to tide them over nutritively until the time when under natural conditions of life they begin to eat other foodstuffs." If this is true of the breast fed baby, how much more important it is that the diet of the arificially fed baby be scrutinized with this in mind. To quote Osborne and Mendel[3]: "A particular case of this kind is that of infant feeding where it is customary to reinforce the supply of calories by diluting top milk and adding milk sugar. Under these circumstances the child is supplied with a food that contains a relatively smaller proportion of the water soluble vitamin than does the original cow's milk. While milk thus modified may contain sufficient vitamin as long as the food intake is normal, if for any reason the child's appetite fails, the vitamin supply is reduced and endless dietary troubles may easily result."

In a study of the weight charts of the babies in our clinic it was observed that in order to get adequate gain in weight it was necessary to give considerably more food than when breast milk is used. Whereas 100[4] calories per kg. is considered sufficient for breast fed babies under 6 months of age, and 90 calories for those more than 6 months old, our babies were receiving from 120 to as high as 150 calories per kilogram on their "theoretical"[5] weight. This experience apparently is borne out by other workers,[6] although these authors do not state whether or not they have based their requirements on the theoretical or the actual weights.

---

3. Osborne, T. B., and Mendel, L. B.: Loc. cit.

4. Langstein, L., and Meyer, L. F.: Säuglingsernährung und Säuglingsstoffwechsel., 2d Ed., Wiesbaden, 1914, p. 98.

5. The following adaptation of Finkelstein's rule was used in estimating the theoretical weight: Birth weight + (600 times age in months) — 300 = weight for the first six months. Birth weight + (500 times age in months) = weight for the second six months.

6. Morse, J. L., and Talbot, F. R.: Diseases of Nutrition and Infant Feeding, New York, The Macmillan Co., 1915, p. 185. Hess, J. H.: Principles and Practice of Infant Feeding, Philadelphia, F. A. Davis Co., 1918, p. 148.

The cases considered were all normal babies many of whom had been in the clinic from the eighteenth day. The feedings consisted of milk mixtures approximating the composition of mother's milk. The dilution system of modification was used, cream and one or more of the usual carbohydrates being added, with sometimes cereal diluents. In all cases the milk preparations were either pasteurized, or boiled one minute in an open kettle. With these mixtures in such liberal quantities, eminently satisfactory gain was achieved, for it was the custom when the child failed to gain to give as much food as was necessary to obtain a normal growth curve. Scurvy was protected against by one-half ounce of orange juice given daily.

If milk is, as suggested, deficient in the antineuritic vitamin it is possible that the large caloric requirement of our babies may be explained by the fact that the additional food, beyond that necessary to meet the needs when breast milk is fed, carried enough of this essential material by adsorption to supply the needs of the child. McCollum[7] and co-workers found in feeding experiments with rats that when the 20 per cent. of lactose used in their purified ration was replaced by an equal amount of dextrin, no growth was secured. These authors attribute their results to a lack of the antineuritic vitamin which had been introduced into the ration with the lactose. Observations, therefore, on the effect of the addition of materials known to contain the antineuritic vitamin were made. During the ward walk those children who were not gaining were selected for a study of the influence of the antineuritic vitamin, without regard to the calory value of the food intake. These babies were receiving from 104 to 126 calories per kilogram on their actual weights and from 90 to 130 calories on their theoretical weights. In each case from one to three periods of vitamin additions were made to the diets, with intervals of about ten days between each. The length of the periods during which the material containing the antineuritic vitamin was added varied from ten to twenty days.

In the first series the antineuritic material was obtained from wheat embryo, the method of extraction being the same as that used in studies pertaining to its influence on growth in animals (rats) fed purified rations. One hundred and eighty gm. of the embryo were extracted with 95 per cent. alcohol for from forty-eight to ninety-six hours. After filtering, 50 c.c. of water were added, the alcohol was distilled off, and the residue made up to 500 c.c. with distilled water. This vitamin containing mixture when tested with Fehling's solution caused a slight reduction; the addition of Lugol's solution produced a faint violet cloud. Subsequent hydrolysis yielded

7. McCollum, E. V., and Davis, M.: J. Biol. Chem. **20**:641, 1915.

a fluid which contained 2.3 per cent. of reducing sugars.[8] Since 50 c.c. were used in each day's feeding the amount of carbohydrate added was equivalent to approximately 1 gm., not enough to affect the growth curve materially.

In a second series (Chart 6) the influence of the alcoholic extract of those vegetables—carrots, turnips and celery— which were used in preparing the vegetable soup referred to below was tested. The vegetables were comminuted, dried in a current of air and treated in the same way as the wheat embryo. The residue of the alcoholic extract of 675 gm. (fresh weight) of vegetable was dissolved in 500 c.c. of distilled water. This mixture contained less than 1 per cent. of reducing sugars. In certain instances 50 c.c. of this were added to a day's feeding, in others, 80 c.c.

DISCUSSION OF RESULTS

It will be seen from a study of the charts that when the vitamin containing extracts were added there was a similar gain in weight in all cases, in spite of the variable factor, such as age, the caloric value of the food and the somewhat different percentage composition of the mixtures fed. In the five charts (Charts 1, 2, 3, 4 and 5) showing the results of the wheat embryo additions, the ages of the children varied from 1½ to 5 months. A similar stimulation of growth took place in older children to whose diet the antineuritic vitamin was added. But since the food conditions in these were not constant, frequently including slightly variable amounts of cereals, their growth curves have not been included.

Apparently the caloric value of the food had little influence on our results, for the food ingestion per kilogram on the actual weight varied between 100 and 120 calories and between 88 and 130 calories on the theoretic weights. Furthermore, in Chart 5 it will be observed that in the same baby the caloric value of the food per unit of weight diminished with the increase in weight, while the growth stimulating influence of the added material was uniform during the periods studied. At the beginning of the investigation this baby (Dorothy G.) was receiving 120 calories on her actual weight, whereas at the beginning of the third period of vitamin addition she was receiving only 100 calories on her actual weight.

In Chart 4 we were able to demonstrate that the slight carbohydrate content of the antineuritic extracts obtained from both the wheat embryo and the vegetables was without influence. The addition of 7 gm. of dextri-maltose did not materially affect the growth curve

8. Benedict, S. R.: J. A. M. A. **57**:1193 (Oct. 7) 1911.

in this case (Jean M.) When, however, the antineuritic vitamin containing extract was added there was a stimulation of growth which apparently was otherwise not possible, for growth had become stationary on the very low food intake—88 calories per kilogram on her theoretical weight—which this baby was receiving at this period.

It is appreciated that if the daily addition of an antineuritic material must be made to the diet of the artificially fed baby some

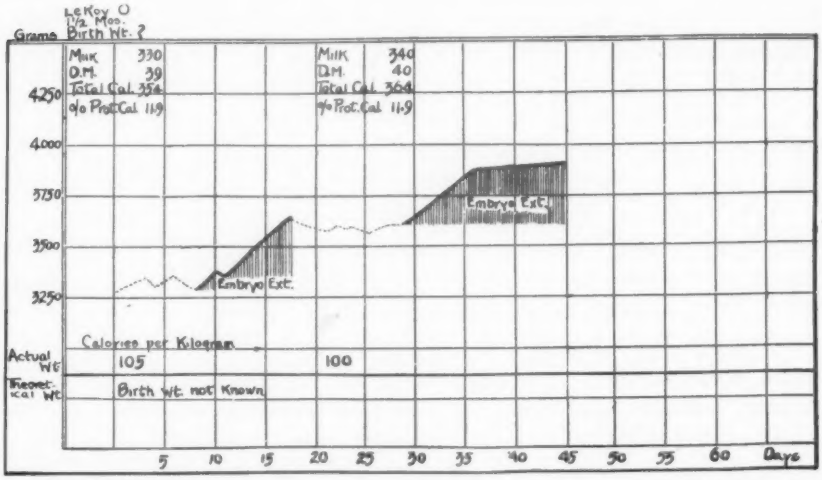

Fig. 1.—The influence of addition, withdrawal and second addition of the wheat embryo extract.

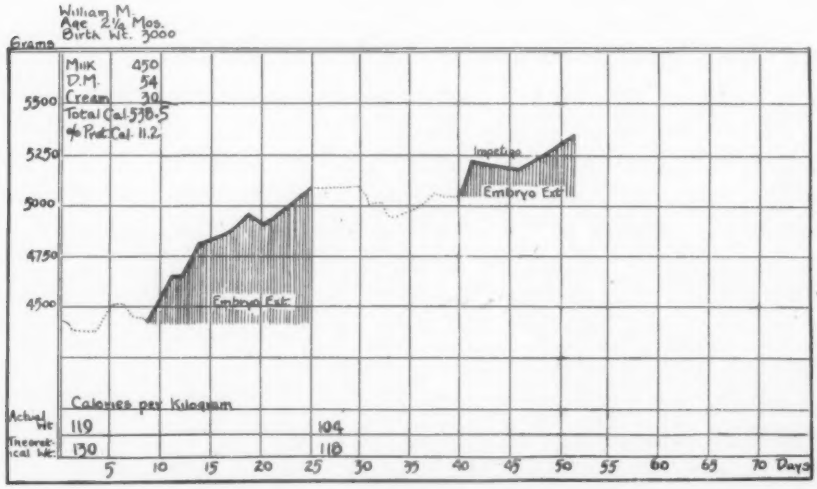

Fig. 2.—When the caloric food intake is considerably above the average, growth stimulation by the embryo extract appears to be somewhat greater. (See Chart 4.)

more easily available source than the wheat embryo extract must be found. Vegetables naturally were first thought of in this connection; and in Charts 6 and 7 are shown curves which demonstrate that the antineuritic material contained in these is a possible source when given in sufficient quantity. In the case of Harriet B. (Chart 6) a slight gain was achieved when 50 c.c. of the prepared vegetable extract were used; and a still more characteristic increase when 80 c.c.

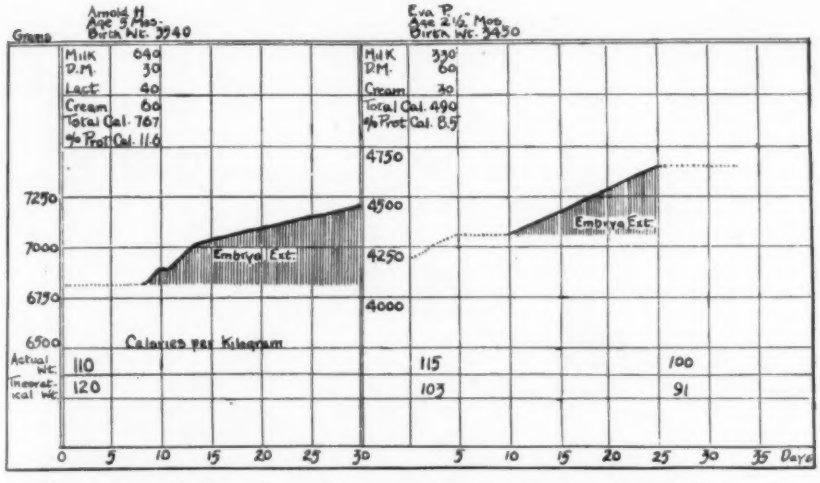

Fig. 3.—Stimulation of growth brought about by the daily addition of the wheat embryo extract following periods of practically stationary weight.

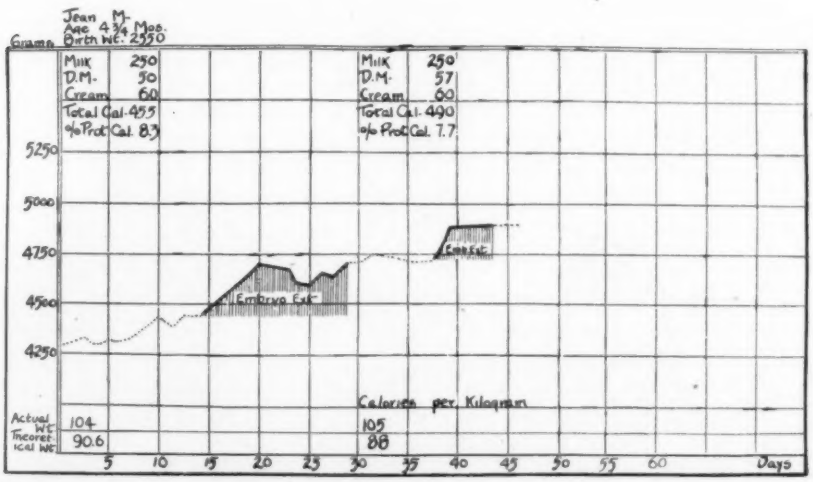

Fig. 4.—With smaller caloric intake—less than 95 per kg.—wheat embryo extract has a lesser influence in bringing about weight increases. The addition of 7 gm. of carbohydrate (28 calories) was without influence on the weight curve.

were included in each day's diet, the material being added to the bottle feedings.

Since our preparations of the antineuritic vitamin are not feasible in routine infant feeding, a special vegetable soup was substituted for the extracted material, and used as a part diluent in the milk formula. This was made of 227 gm. of turnips, 278 gm. of carrots and 170 gm. of celery. These were comminuted and cooked until

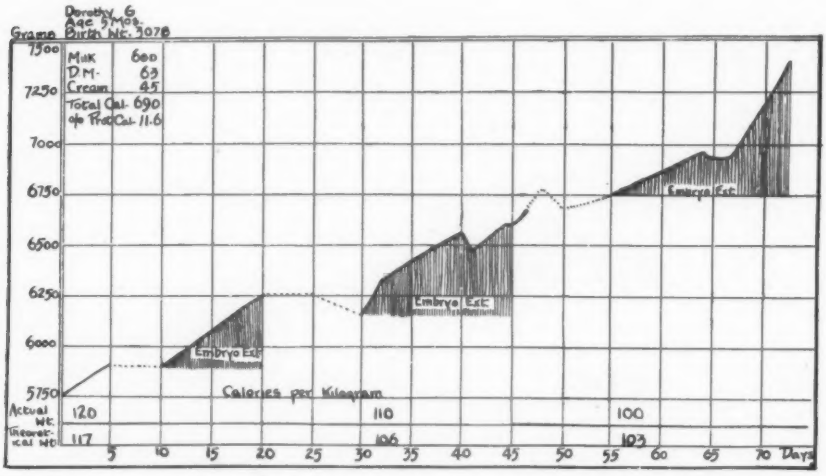

Fig. 5.—Favorable influence of wheat embryo extract addition during three successive periods.

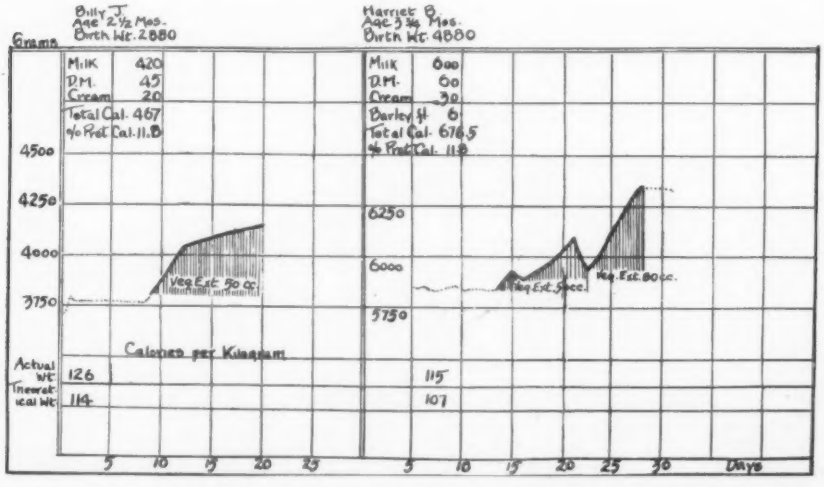

Fig. 6.—The alcoholic extract of vegetables had an influence similar to that of the wheat embryo extract. In the case of Harriet B., 80 c.c. seemed somewhat more efficient than 50 c.c.

very soft, with enough water to cover. The material was then strained, thereby removing practically all of the cellular material. From the 675 gm. of fresh vegetables there was obtained 500 c.c. of soup.

In Chart 7, 50 c.c. of this vegetable soup were found to be insufficient. When double this amount was added growth was markedly stimulated. With the use of the vegetables, it is appreciated that another factor has been introduced, namely, that of the inorganic salts. What part these salts play in the growth curve and what their effect on the child is, remains to be determined. There is no doubt, however, that at least a part of the growth stimulation has been due to the antineuritic vitamin.

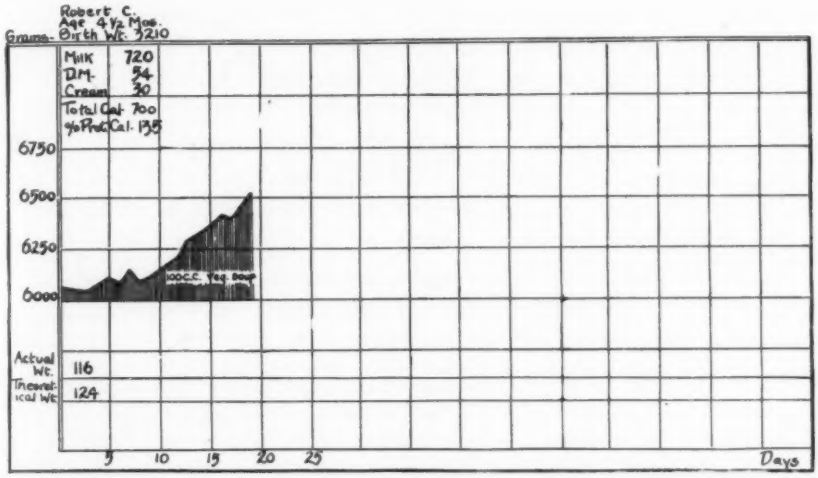

Fig. 7.—Vegetable soup used as part diluent in the milk modification also stimulated growth. During the first part of the investigation period 30 c.c. were added, whereas during the second part 100 c.c. were used.

It should be borne in mind that the infants reported here have all been normal babies and therefore their antineuritic requirements were presumably small. However, this should not affect the validity of the findings for in other cases in which this substance has been added where there was manifestly under nutrition, growth has been stimulated. Since other therapeutic measures were included in the treatment of these cases it has not seemed pertinent to include their charts in this report. Our results here are comparable apparently to those of Eddy and Roper[9] who found that the antineuritic vitamin obtained from pancreas stimulated growth in children suffering from marasmus.

9. Eddy, W. H., and Roper, C. J.: Am. J. Dis. Child. **14**:189 (Sept.) 1917.

The influence of the addition of the antineuritic vitamin on the growth of older children has been indicated by Hess.[10] In studies pertaining to infantile scurvy, a cereal composed of wheat middlings and farina was used. "In certain instances," he states, "improvement was immediate and striking; there was a gain in weight for the first time in many months." The effect of this material, however, was in no way comparable to that produced by the addition of orange juice. It is probable that Hess' babies were suffering from a lack of the antineuritic as well as the antiscorbutic vitamin. In a later attempt to find a substitute for orange juice as an antiscorbutic, Hess[11] in turn used both yeast and wheat germ preparations. While his work indicated that these apparently have no antiscorbutic value, when they were added to the diet of some older babies and children from 1½ to 2 years old, there was marked stimulation of growth. It would appear these children also had been receiving a diet furnishing too little of the antineuritic vitamin.

CONCLUSIONS

From the results of the investigation it would seem that the following conclusions are justified:

1. The addition of the antineuritic vitamin obtained from wheat embryo to the diet of babies supplied with food furnishing an adequate number of calories stimulated growth.

2. The beneficial influence of adding a specially prepared vegetable soup in sufficient quantity as part diluent in the milk modifications for infants is apparently due to the presence of the antineuritic vitamin contained therein. Both the alcoholic soluble material of the dried soup vegetables, and the water extract (soup) stimulated growth.

3. The fact that the artificially fed infant requires a larger amount of food than the breast fed infant appears to be due to the relative paucity of diluted cow's milk in the antineuritic vitamin.

4. It is probable that failure to gain in infants and young children is often the result of an insufficient amount of the antineuritic vitamin in the food. The diets of the young, we believe, should be more carefully scrutinized with this in mind.

---

10. Hess, A. F.: J. A. M. A. **65**:1003 (Sept. 18) 1915.
11. Hess, A. F.: Am. J. Dis. Child. **13**:98 (Jan.) 1917.

CHEMICAL EXAMINATION OF THE BLOOD IN CHILDREN

A STUDY OF ONE HUNDRED AND FORTY-NINE CASES *

HENRY DWIGHT CHAPIN, M.D.
AND
VICTOR CARYL MYERS, PH.D.
NEW YORK

The chemical examination of the blood has yielded such valuable information in the diagnosis, prognosis and treatment of constitutional diseases in the adult that it has seemed worth while to present the data on infants and children which we have been collecting during the past five years. Although various problems of interest in pediatrics have been attacked with the aid of chemical methods of blood analysis, the information available is somewhat fragmentary. Nevertheless, a number of fundamental facts have been obtained. In general, the findings have been quite similar to those found in the adult, although it would appear that there is a tendency toward slightly lower figures.

In the case of blood sugar, Bass[1] has shown that the values are essentially the same as those found in the adult, and Schultz and Pettibone[2] have made somewhat similar observations regarding the nonprotein, urea and amino acid nitrogen in a few cases. Tileston and Comfort[3] come to some very interesting conclusions as a result of their study of the total nonprotein nitrogen and urea of the blood and the phenolsulphonephthalein excretion in children. They point out that their investigations of the blood and phenolsulphonephthalein excretion would appear to indicate a better secreting capacity of the child's kidney as compared with the adult. Their series of fifty-one cases includes three nephritics, two of whom show urea retention. They conclude that the nonprotein and urea nitrogen are of great assistance in the diagnosis of uremia and as a guide to the treatment of nephritis, but that these tests are inferior to other methods in the diagnosis of nephritis, because in many nitrogen retention is not apparent. They believe that in the diagnosis of nephritis the phenolsulphonephthalein

---

* Read before the Section on Diseases of Children at the Seventieth Annual Meeting of the American Medical Association, Atlantic City, N. J., June, 1919.

* From the Department of Diseases of Children and the Laboratory of Pathological Chemistry, New York Post Graduate Medical School and Hospital.

1. Bass, M. H.: Am. J. Dis. Child. **9**:63 (Jan.) 1915.
2. Schultz, F. W., and Pettibone, C. J. V.: Am. J. Dis. Child. **10**:206 (Sept.) 1915.
3. Tileston, W., and Comfort, C. W.: Am. J. Dis. Child. **10**:278 (Oct.) 1915.

test probably shows the degree of impairment of renal function better than any other method. Leopold and Bernhard[4] report observations on the nonprotein and urea nitrogen, uric acid, creatinin and phenolsulphonephthalein excretion of sixty-six patients, sixteen being nephritics. Only two of the latter group showed urea nitrogen figures above 20 mg. The figures for creatinin and uric acid were normal. Their figures on patients free from renal disease were considered essentially the same as those found in the adult. The series of observations on the nonprotein nitrogen and creatinin presented by Vedder and Johnston[5] contains eight cases of nephritis, three of which showed an increase in the nonprotein nitrogen, but no increase in creatinin. Hill[6] has reported urea nitrogen figures on twelve nephritics, seven of whom show figures ranging from 21 to 46 mg. He concludes, however, that most of the

TABLE 1.—CASE 1, R. K., ACUTE NEPHRITIS WITH RECOVERY *

Date, 1918	Blood Analyses				Phenolsulphonephthalein, 2 Hour Output, per Cent.
	Urea N, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c	Sugar, per Cent.	CO_2 Combining Power, C.c. per 100	
Feb. 2	50	2.5	0.117	50	
5	29	2.9	0.107	..	22
8	15	2.2	0.105		
11	..	...	....	..	71
12	17	2.9	0.097		
15	15				
16	..	...	.....	..	70

* Acute nephritis in a girl, 14½ years of age, following an attack of tonsillitis two weeks previously; one examination of the urine showed specific gravity 1.025, a small amount of protein and many hyaline and granular casts.

chronic cases of nephritis in children are so mild and so slowly progressive that there is no urea retention, or at least not enough to give any information of value, and that the test applies more particularly to the hypertensive cases with contracted kidneys, seen in the adult. Regarding the blood uric acid, Sedgwick and Kingsbury[7] have made the very interesting observation that it is high during the first three or four days of life, in harmony with the high uric acid excretion during that period.

The subject of the acidosis occurring with diarrhea is one that has recently received considerable attention, especially at the hands of Howland and Marriott,[8] and Schloss and Stetson.[9] It was the topic

4. Leopold, J. S., and Bernhard, A.: Am. J. Dis. Child. **11**:432 (June) 1916.
5. Vedder, B. S., and Johnston, M. R.: Am. J. Dis. Child. **12**:136 (Aug.) 1916.
6. Hill, L. W.: Am. J. Dis. Child. **14**:267, 1917; **17**:270, 1919.
7. Sedgwick, J. P., and Kingsbury, F. B.: Am. J. Dis. Child. **14**:98, 1917.
8. Howland, J., and Marriott, W. McK.: Am. J. Dis. Child. **11**:309 (May) 1916; also Bull. Johns Hopkins Hosp. **27**:63 (March) 1916.
9. Schloss, O. M., and Stetson, R. E.: Am. J. Dis. Child. **13**:218, 1917.

of a paper before this Section in 1916 by one of us in association with Pease.[10] Thirty-four cases were reported at that time, with Van Slyke carbon dioxid combining power values in twelve cases. The lowest result obtained was 22, and the average 28. Howland and Marriott have shown that the acidosis found in many cases of severe diarrhea not of the ileocolitis type is not due to the presence of acetone bodies, but apparently is due to deficient excretion of acid phosphate by the kidneys. The administration of sodium bicarbonate will often bring about a cessation of the almost characteristic hyperpnea and cause the laboratory tests to give the results that are found with normal infants. Nevertheless, the child may die. Schloss and Stetson have applied the Van Slyke method for the determination of the carbon dioxid combining power of the blood plasma to a quite extensive series of cases.

TABLE 2.—CASE 2, F. F., ACUTE NEPHRITIS WITH RECOVERY *

Date, 1917-18	Blood Analyses					Phenolsulphonephthalein, 2 Hour Output, per Cent.
	Creatinin, Mg. to 100 C.c.	Urea N, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Sugar, per Cent.	CO_2 Combining Power. C.c. per 100	
Dec. 18	6.1	106	11.4	0.106		
19	...	..	....	.....	..	16
21	5.9	93	11.2	0.150	54	
24	...	..	....	.....	..	44
26	...	..	....	.....	..	42
27	4.2	21	5.0	0.135		
Jan. 2	4.0	23	....	0.096		
4	3.7	26	....	0.090	..	57
8	3.8	28	....	0.122		
Oct. 30	...	10				

* A boy, 8 years of age, was admitted to the hospital December 17 following suppression of urine for three days, apparently due to an injury. He had convulsions, edema of the face and vomiting for four days. He improved rapidly and left the hospital January 17. He is apparently well at the present time.

In twenty-seven normal cases the figures ranged from 46 to 63 c.c. carbon dioxid per 100 c.c. of plasma. In seventeen out of nineteen cases of diarrhea with toxic symptoms the figures ranged from 13 to 38. The acetone bodies of the blood have been studied by Moore[11] in Howland's laboratory. In cases of diarrhea without ileocolitis there is only a moderate increase in acetone bodies, while with ileocolitis the amount of acetone bodies is very large.

It is of further interest that Howland and Marriott[12] have observed that in infantile tetany there is a decrease in the calcium content of the blood, and that the condition is greatly improved by the continued administration of calcium.

10. Chapin, H. D., and Pease, M. C.: J. A. M. A. **67**:1351 (Nov. 4) 1916.
11. Moore, F.: Am. J. Dis. Child. **13**:244 (Sept.) 1916.
12. Howland, J., and Marriott, W. McK.: Quart. J. Med. **11**:289, 1918.

Our own observations comprise a study of 149 miscellaneous cases occurring among infants and children. The older children were patients in the medical wards of the hospital and are included through the courtesy of Drs. Chace and Kast of the medical department. The study includes observations of the sugar, urea, creatinin and, in some cases, of the uric acid and carbon dioxid combining power, and the phenolsulphonephthalein test on the urine. The sugar was estimated by a modification of the Lewis and Benedict[13] method, the urea, creatinin and uric acid by modified (Folin) methods as already described[14] and the carbon dioxid according to the method ot Van Slyke.[15]

TABLE 3.—CASE 3, P. L., CHRONIC NEPHRITIS WITH ONLY SLIGHT NITROGEN RETENTION.*

Date, 1916	Blood Analyses				Phenol-sulphone-phthalein, 2 Hour Output, per Cent.
	Urea N, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Sugar, per Cent.	
Mar. 28	..	...	...	.....	Trace
30†	18	1.7	4.1	0.118	
Apr. 10	..	...	...	.....	8
12	14	1.2	...	0.120	
May 18	..	...	...	.....	8
June 8	..	...	..	.....	5
9	28	1.8			
July 13	..	...	...	.....	4
14	15	1.6	...	0.126	
26	..	...	...	.....	6
Aug. 7	..	...	...	.....	3
15	22	2.1	4.5	0.135	
Sept. 15	..	..	...	.....	6

* A girl, 10 years of age, was admitted to the hospital March 27, 1916, with a history of general edema for the preceding twenty months. Urinary findings: specific gravity from 1.012 to 1.020, moderate amount of protein, casts always present and sugar generally present, although not always, from 0.5 to 1.0 per cent. Double decapsulation of the kidneys was done August 1. The patient left the hospital September 27 essentially unimproved, but is apparently much improved at the present time.

† Abdominal fluid.

In the adult, normal values for the blood sugar may be given as 0.09 to 0.12 per cent., urea N. 12 to 15 mg. per 100 c.c., creatinin from 1 to 2 mg. and uric acid from 1 to 3 mg. For perfectly normal children the figures probably fall within the same limits, although, if anything, the average is slightly lower. The carbon dioxid combining power has been found to be somewhat lower in children than in adults, as pointed out above, from 45 to 65 c.c. per 100 c.c. In twelve perfectly normal children, Sawyer, Stevens and Baumann[16] found an average of 54.

With this scheme of blood analysis the sugar serves to indicate the carbohydrate tolerance; the urea, creatinin and uric acid, especially

13. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:147 (Feb.) 1916.
14. Myers, V. C., and Fine, M. S.: Arch. Int. Med. **17**:570 (April) 1916.
15. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:289, 347 (June) 1917.
16. Sawyer, M., Stevens, F. A., and Baumann, L.: Am. J. Dis. Child. **15**:1 (Jan.) 1918.

the urea, the functional activity of the kidneys; while the carbon dioxid covers the condition of acidosis. The creatinin is of very great prognostic value in cases of advanced nephritis in the adult,[17] but is of comparatively little value in the type of nephritis encountered in children, only three cases in our series giving creatinin figures over 5 mg. As has been pointed out, uric acid appears to be the first nitrogenous waste product retained in nephritis,[14] and this seems to be borne out by the few observations recorded below, but its usefulness here is quite inferior to the urea.

In Tables 1 to 6 are presented data from thirty-eight cases of nephritis. Data in the first five cases are shown individually as illustrating types of cases that may be encountered. The first two cases are acute cases in which recovery resulted. In Case 1 there was only

TABLE 4.—CASE 4, M. C., CHRONIC NEPHRITIS WITH ONLY MODERATE NITROGEN RETENTION *

Date, 1916	Blood Analyses				Phenolsulphonephthalein, 2 Hour Output, per Cent.
	Uric Acid, Mg. to 100 C.c.	Urea N, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Sugar, per Cent.	
June 20	...	43	2.7	0.148	18
23	6.6	50	3.1	0.117	
27	8.0	36	2.7	0.132	
July 5	...	39	2.2	0.116	26
11	7.0	70	3.0	0.165	
18	6.3	60	2.8	0.165	
21	6.3	53	2.9	0.129	
25	4.4	49	3.1	0.110	
28	6.8	50	2.3	0.108	
Aug. 7	7.2	43	3.9	0.114	

* Patient, a boy 11 years of age, was admitted June 19, 1916, and was discharged clinically improved August 18. He had generalized edema, convulsions every hour all day on admission. He was somewhat anemic. The urine showed a consistently low specific gravity, from 1.006 to 1.008, with from a trace to a large amount of protein. He was kept on a salt free diet for one year after leaving the hospital. He is much improved at the present time.

moderate urea retention, no creatinin retention and practically no acidosis. In Case 2 there was a marked retention of all three waste products, the creatinin found being the highest we have observed with ultimate recovery. Case 3, a chronic case, in which there was marked edema and only slight nitrogen retention, presented the interesting feature of a fairly constant mild glycosuria, apparently of renal origin. The phenolsulphonephthalein output was uniformly low. Two quite similar cases have been encountered in the wards of the hospital in adults, one of which has been reported by Bailey.[18] In the three years that have elapsed since Case 3 left the hospital, considerable improvement has apparently taken place. Case 4 was likewise a chronic case with marked edema, but showed considerably more nitrogen retention

17. Myers, V. C., and Killian, J. A.: Am. J. Med. Sc. **157**:674 (May) 1919.
18. Bailey, C. V.: Am. J. Med. Sc. **157**:221 (Feb.) 1919.

than the preceding case. Although the patient improved clinically, the urea retention was unchanged when he left the hospital. He was kept on a salt-free diet for one year after he left the hospital, and is apparently considerably improved at the present time, although with a cold he still shows edema. In Case 5, a history of nephritis of more than two years' standing was obtained. The first blood examination in this case was made about five months before the death of the patient. Although at this time there was only moderate urea retention, the creatinin had already reached a high figure, 5.4 mg. Nevertheless, there was considerable clinical improvement and a marked drop in the nitrogen retention, the patient returning home. She was readmitted to the hospital much worse two months later, one blood examination having been made in the interval. She died in the hospital a month later with blood findings typical of interstitial nephritis.

TABLE 5.—CASE 5. A. F., CHRONIC NEPHRITIS WITH MARKED NITROGEN RETENTION *

Date, 1918	Blood Analyses				Phenol-sulphone-phthalein, 2 Hour Output, per Cent.
	Creatinin, Mg. to 100 C.c.	Urea N, Mg. to 100 C.c.	Sugar, per 100 C.c.	CO_2 Combining Power, C.c. per 100	
Aug. 21	5.4	42	0.142	46	
23	....	...	.....	..	25
Sept. 3	3.2	20	0.136		
Oct. 11	3.0	30	0.141		
Nov. 30	....	...	.....	..	Trace
Dec. 3	7.9	161	0.212		
11	13.6	217	.....	48	

* Patient was first admitted to the hospital for removal of adenoids and tonsils, May 3, 1916, then 10 years of age. Her urine at that time showed specific gravity 1.005, a moderate amount of protein, and occasional granular casts. She was readmitted to the hospital August 19, 1918, complaining of headaches, convulsions and blindness. She left improved September 16; was readmitted November 18 complaining of vomiting three times daily. She died December 14.

Table 6 contains observations in thirty-three cases arranged according to the magnitude of the blood urea. The table includes those cases in which a clinical diagnosis of nephritis was made, and eight other cases with urea figures over 20 mg. As has been pointed out by one of us,[19] any severe disease, such as pneumonia or acute enteritis, may irritate the kidney to the point of inflammation in striving to eliminate noxious products. From the studies of Squier and Myers,[20] and Kast and Wardell,[21] it would appear that urea nitrogen figures above 20 mg. may be regarded as evidence of impairment of renal function. In certain cases this may be true of figures above 15 mg. In the above series of thirty-eight cases, exactly two-thirds showed urea nitrogen figures

19. Chapin, H. D., and Pisek, G. R.: Diseases of Infants and Children, New York, 1909, p. 456.
20. Squier, J. B., and Myers, V. C.: J. Urol. **2**:1, (Feb.) 1918.
21. Kast, L., and Wardell, E. L.: Arch. Int. Med. **22**:581 (Nov.) 1918.

TABLE 6.—Miscellaneous Cases of Nephritis in Children

Case	Age, Years	Sex	Date	Blood Analyses: Urea N, Mg. to 100 C.c.	Blood Analyses: Creatinin, Mg. to 100 C.c.	Blood Analyses: Uric Acid, Mg. to 100 C.c.	Blood Analyses: Sugar, per Cent.	Phenolsulphonephthalein, 2 Hr. Output, %	Clinial Diagnosis; Outcome
6. M. O.	8	♀	5/28/15	90	11.1	13.0	.....	..	Chronic nephritis, double; decapsulation; death
7. W. S.	3	♂	3/30/15	70	4.8	11.8	0.135	..	Acute nephritis; recovery
8. A. W.	4½	♂	3/30/15	59	3.1	5.6	0.153	..	Acute nephritis; recovery
9. A. T.	¾	♂	3/19/18	55	3.3	....	0.120	..	Pneumonia; death
10. R. L.	2	♀	8/29/16	42	....	....	0.159	..	Pyelonephritis; death
			9/30/16	34	....	9.4			
			10/ 3/16	10	2.2	....	0.120		
11. D. K.	5	♂	3/30/17	9	2.5	....	0.112	..	Parenchymatous nephritis; improvement
			5/ 4/17	16	2.8	....	0.114		
			5/18/17	11	....	3.3			
12. M. Z.	7½	♂	4/10/17	30	3.3	....	0.105	42	Bronchopneumonia; recovery
			10/ 9/17	27	2.7	....	0.099		
13. L. B.	7	♂	10/16/17	16	1.8	....	0.100	36	Exophthalmic goiter; improvement
			11/ 2/17	11	2.2	....	0.126		
14. M. K.	8	♂	7/13/17	26	2.8	....	0.129	..	Purpura hemorrhagica; death
15. C. A.	6	♂	4/27/17	25	2.1	....	0.102	..	Subacute parenchymatous nephritis; improvement
16. I. B.	6	♂	8/11/16	25	....	....	.....	..	Acute nephritis; pericarditis with effusion; death
17. D. W.	7½	♂	4/30/17	24	....	....	.....	..	Hydronephrosis plus infection; improvement
			5/ 8/17	22	2.5	....	0.123	40	
18. P. T.	6	♂	8/31/17	23	2.8	....	0.120	31	Parenchymatous nephritis; chronic hydrocephalus; no improvement
19. E. W.	4	♀	9/22/15	23	1.8	2.5	0.100	37	Nephritis; improvement
20. M. L.	15	♀	1/ 4/18	23	2.8	....	0.136	41	Duodenal ulcer; endocarditis; improvement
21. F. W.	13	♂	6/23/16	22	1.4	4.2	0.120	38	Chronic diffuse nephritis; improvement
22. I. G.	11	♂	3/ 4/19	22	1.8	....	0.109	..	Endocarditis; death
23. B. L.	12	♂	10/12/15	21	2.8	3.2	0.114	65	Pylorospasm; recovery
			11/19/15	..	1.5	....	0.070		
24. A. S.	5	♀	10/28/16	21	2.1	....	0.114	..	Raynaud's disease; improvement
25. E. M.	4½	♂	7/ 7/18	21	2.1	..	0.110	..	Acute nephritis; improvement
26. I. N.	12	♂	11/19/18	17	2.5	....	0.100	30	Acute nephritis; improvement
27. B. L.	5	♀	1/23/17	..	2.0	....	0.130	..	Acute parenchymatous nephritis; improvement
			2/ 2/17	17	1.9	....	0.111		
28. H. S.	4½	♂	3/ 9/17	17	1.1	....	0.108	..	Acute parenchymatous nephritis; recovery
			3/16/17	14	1.9	....	0.099		
29. D. W.	4	♂	8/31/17	16	2.6	....	0.144	..	Parenchymatous nephritis; improvement
30. S. G.	4½	♀	2/11/19	15	....	....	.....	..	Acute nephritis; death
31. V. T.	11	♂	3/26/18	13	2.0	....	0.105	47	Chronic interstitial nephritis; improvement
			5/ 9/18	13	2.5	....	0.133	44	
32. V. D.	5	♂	8/ 8/17	13	4.0	....	0.102	..	Parenchymatous nephritis; improvement; cholesterol, 0.326%
33. L. F.	12	♀	9/24/15	13	1.7	....	0.097	53	Chronic parenchymatous nephritis; improvement
34. C. O'R.	10	♀	4/28/16	12	2.9	....	0.123	36	Decompensated heart and interstitial nephritis; improvement
								62	
35. J. F.	3	♂	10/29/15	12	....	....	.....	..	Nephritis; improvement
36. F. S.	5	♂	5/11/17	11	2.7	....	0.126	45	Tuberculosis of hip with abscess; acute nephritis; death
37. A. K.	3	♂	5/ 1/17	9	3.2	....	0.129	..	Acute nephritis; recovery
38. C. T.	11	♂	1/ 7/19	9	....	....	0.110	..	Acute nephritis following influenza; death

above 20 mg. The findings in the remaining cases were essentially normal. The phenolsulphonephthalein excretion appears to harmonize very well with the urea findings. The first four cases in Table 6, in which uric acid estimations were made, show a marked increase, while the creatinin is abnormally high in only the first two cases. The blood sugars are normal except in the cases with marked nitrogen retention.

TABLE 7.—CASES ILLUSTRATING ACIDOSIS IN CHILDREN

Case	Age	Sex*	Date	Blood Analysis			Diagnosis; Remarks; Outcome
				CO_2 Combining Power, C.c. per 100	Sugar, per Cent.	Creatinin, Mg. to 100 C.c.	
39. A. N.	2 mo.	♀	9/26/15	22	0.09	0.9	Gastro-enteritis; acidosis; death
40. W. R.	3½ mo.	♂	1/20/15	24	0.10	2.1	Gastro-enteritis; acidosis; death
41. Y. W.	6 wks.	♀	11/ 9/17	24	....	...	Acute gastro-intestinal acidosis; death
42. M. K.	10 mo.	♂	10/19/17	25	....	...	Infectious diarrhea; death
43. J. T.	4 mo.	♂	10/13/15	26	0.10	1.4	Malnutrition; recovery
44. H. C.	8½ mo.	♂	11/15/15	28	0.09	1.1	Malnutrition; acidosis; recovery
45. J. M.	1 yr.	♀	11/ 3/17	28	....	...	Gastro-enteritis and rickets; vomiting; improvement
46. M. B.	4½ yrs.	♂	11/29/17	29	....	...	Postoperative hernia, CO_2 3 days after operation; large amount of acetone in urine; recovery
47. J. F.	5 mo.	♂	4/15/16	30	0.08	...	Gastro-enteritis; acidosis; death
48. P. K.	10 mo.	♀	11/24/15	33	0.11	0.9	Lobar pneumonia; acidosis; death
49. E. B.	9 mo.	♂	11/20/15	35	....	1.2	Gastro-enteritis, otitis media; acidosis; recovery
50. R. S.	6 mo.	♀	3/17/16	36	0.10	2.2	Gastro-enteritis; acidosis; death
51. S. K.	1 yr.	♂	12/14/15	36	0.08	1.0	Amaurotic family history, acidosis; recovery
52. W. H.	9 mo.	♂	10/10/15 2/ 2/16	38 40	0.08 0.09	1.3 1.8	Malnutrition; acidosis; recovery and bronchopneumonia; acidosis; death
53. W. W.	4½ yr.	♂	4/ 1/16	41	0.09	...	Gastro-intestinal toxemia; acidosis; recovery
54. R. E.	7 mo.	♂	2/ 6/16	42	0.08	...	Malnutrition; acidosis; death

We are under obligations to Dr. M. C. Pease for many of the observations in this table.
* In this column, ♂ indicates male, ♀ female.

It would appear from the above series of nephritis cases that marked nitrogen retention was quite uncommon in children, and from the rather favorable outcome in Cases 1, 2, 3, 7 and 8 that recovery was much more likely to occur in children than in adults. Only two patients in the series died with findings typical of interstitial nephritis (Cases 5 and 6), girls 12 and 8 years of age, respectively. As a result of our observations we may conclude that the blood urea is a most excellent index of the severity of nephritis in children. In other words, it is a very useful prognostic test, although of much less value diagnostically. It should be noted that proteinuria was present in practically all cases.

The data on the carbon dioxid combining power of the blood in the acidosis of diarrhea presented in Table 7 merely serve to illustrate the low figures which may be encountered. As previously pointed out, Chapin and Pease, and Schloss and Stetson[9] have given interesting discussions of this subject.

Table 8 furnishes blood sugar observations on six diabetic children. Although diabetes is quite uncommon in children, there is nothing especially unusual in these observations, or different than might be

TABLE 8.—DIABETES IN CHILDREN

Case	Age, Years	Sex*	Date	Blood Analyses			Urine		Remarks
				Sugar, per Cent.	CO_2 Combining Power, C.c. per 100	Urea N, Mg.	Sugar, per Cent.	Acetone Bodies	
55. B. B.	14	♂	3/10/14	0.79	..	..	8.7	++	Four years' duration, died
56. A. v. N.	12	♂	6/21/16	0.290	47	12	...	....	Diabetes of 14 mos. duration; in hospital twice, left clinically improved each time
			7/ 6/16	0.236	..	11			
			7/ 8/16	0.144	52				
			7/18/16	0.245	38				
			7/22/16	0.180	51				
			7/25/16	0.198	58	..	—	++	
			9/29/16	0.183	..	..	—	+	
			10/ 3/16	0.258	..	..	tr.	—	
			10/ 6/16	0.235	..	..	—	++	
57. S. B.	15	♂	6/26/17	0.336	..	16	5.0	++	Diabetes of 2 years' duration; left hospital clinically improved
			6/28/17	0.294	44	..	5.0	+	
			6/29/17	0.350	46				
			7/ 3/17	0.220	..	9	2.5	+	
			7/ 6/17	0.230	56	..	—	—	
			7/10/17	0.216	56	..	—	—	
			7/13/17	0.288	59	..	1.8	+	
			7/17/17	0.188	57	..	—	—	
			7/20/17	0.192	52	..	—	—	
58. A. G.	7	♀	12/ 2/18	0.492	..	..	1.7	++	Six months' duration; died same day
59. S. M.	13	♂	12/13/18	0.344	..	..	3.0	+	Left improved
60. M. B.	10	♀	2/ 8/19	0.166	..	..	4.0	....	Left improved
			2/18/19	0.128	..	13	—	+	

* In this column, ♂ indicates male, ♀ female.

found in the adult. We have taken occasion to emphasize[22] that the absence of glycosuria is not always a safe criterion of the absence of hyperglycemia, the condition which after all the clinician is trying to relieve. An inspection of the data in Cases 56 and 57 shows that the blood sugar was frequently above 0.2 per cent. when the urine was qualitatively free from sugar.

The eighty-nine miscellaneous cases analyzed in Table 9 present comparatively little of pathologic interest. It may be noted, however, that in Case 85, with lymphatic leukemia, a blood uric acid of 10 mg. was noted.

22. Bailey, C. V.: Arch. Int. Med. **23**:459 (April) 1919.

TABLE 9.—Observations on Miscellaneous Conditions in Children

Case	Age, Years	Sex*	Date	Blood Analyses					Phenol-sulphone-phthalein, 2 Hour Output, per Cent.	Diagnosis; Outcome
				Urea N, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Sugar, per Cent.	CO_2 Combining Power, C.c. to 100		
61. A. P.	14	♀	3/ 8/18	15.5	2.5	2.0	0.125	..	84	Rheumatic fever; heart murmurs; endocarditis; improvement
62. I. K.	9	♂	6/ 8/17	12.6	2.6	...	0.126	..	62	Rheumatism and mitral lesion; systolic murmur; improvement
63. A. U.	14	♀	5/17/18	9.3	2.6	..	0.133	..	32	Bacteremia; casts and albumin; death
64. M. K.	10	♂	3/11/19	11.3	..	...	.....	..	91	Tuberculous peritonitis; secondary anemia; death
65. G. P.	8	♂	11/23/17	15.8	2.0	..	0.141	..	....	Tuberculous peritonitis and appendicitis; improvement
66. V. D.	6	♂	11/19/17	13.0	4.0	...	0.102	..	....	Tuberculous peritonitis and pleurisy; cholesterol, 0.326 per cent.; improvement
67. R. M.	15	♀	3/ 1/18	11.0	2.4	...	0.106	..	65	Enteroptosis; improvement
68. L. F.	14	♀	5/ 9/18	15.8	2.3	...	0.150	..	....	Meningitis; cure
69. M. R.	14	♀	2/26/18	19.0	2.8	...	0 097	..	77	Chronic appendicitis; no improvement
70. L. R.	12	♀	6/26/18	18.0	2.0	...	0 129	..	....	Sarcoma of left kidney; no improvement
71. M. M.	13	♀	4/ 8/19	9.7	2.3	...	0.111	..	....	Internal hemorrhoids; gastric neurosis; no improvement
72. S. E.	5½	♂	4/29/15	....	...	...	.....	..	26	Lobar pneumonia with effusion; nephritis; improvement
73. I. K.	11	♀	6/ 4/18	18.0	1.9	...	0.123	..	.. ..	Chorea and atypical Friedreich's ataxia; improvement
74. G. H.	13	♀	4/ 8/19	15.6	2.3	..	0.089	..	....	Acute chorea; improvement
75. A. M.	12	♀	4/ 8/19	12.9	...	...	.....	..	84	Acute chorea; improvement
76. E. K.	13	♀	8/24/15	11.0	1.0	4.4	0.10	..	45-33	Chorea; acute parenchymatous nephritis; improvement
			8/17/15	16.0	1.9	2.7	0.08	..		
77. E. S.	10	♂	9/ 6/16	11.0	1.4	...	0.117	..	....	Chorea; improvement
78. T. W.	12	♂	9/ 2/17	9.3	2.5	...	0.220	..	...	Sydenham's chorea; hypertrophied tonsils and adenoids
				14.0	2.8	..	0.138		59	Chorea; improvement
79. M. M.	6	♂	10/19/17	10.1	2.2	...	0.087	..	....	Chorea; improvement
80. R. A.	8	♂	11/ 8/17	13.5	2.1	...	0.120	..	62	Idiopathic epilepsy; trace albumin in urine; unchanged
81. W. S.	15	♂	6/24/15	15.0	1.6	6.3	0.144	..		
82. W. K.	5	♀	11/30/17	14.0	2.3	...	0.126	..	....	Epilepsy; no improvement
83. F. F.	10	♂	8/28/16	8.4	...	2.4	.....	..	....	Typhoid fever; cure
84. T. O.	15	♂	6/24/15	10.0	1.4	3.5	0.116	..	...	Acromegaly (?); no improvement
85. S. R.	13	♂	8/15/15	17.0	2.4	10.0	0.117	..	..	Lymphatic leukemia; death
86. R. E.	2/12	♂	2/ 9/15	17.0	1.5	6.3	0.162	30	.. ..	Stricture of anus; operation; cure
			2/10/15	14.0	2.8	4.6	0.108	42		
87. R. S.	6/12	♀	3/ 2/15	15.0	2.2	3.3	0.102	39	....	Gastro-enteritis, bronchopneumonia; death
88. M. S.	3	♂	11/ 2/17	....	2.2	...	0.117	..	...	Chronic gastro-enteritis
89. M. K.	3/12	♂	11/ 9/17	....	...	..	.....	46	...	Chronic gastro-enteritis; improvement
90. M. B.	1 2/12	♀	2/ 6/17	9.0	1.5	...	0.140	..	....	Acute gastro-enteritis; cure

91.	I. B.	9	♂	10/30/17	14.1	2.2	...	0.129	..	....	Cyclic vomiting
92.	R. E.	1	♂	3/19/18	10.1	1.1	..	0.107	..	....	Diphtheria; no improvement
93.	C. H.	1 4/12	♂	6/ 7/18	15.2	1.2	...	.....	..	....	Secondary anemia; improvement
94.	F. O.	2/12	♂	11/16/17	13.0	...	..	0.124	..	....	Tetany, acidosis; acetone in urine +++; convulsions; cure
95.	R. K.	3	♂	2/28/17	15.8	...	...	.....	..	....	Rickets; no improvement
96.	J. D.	4	♂	1/11/18	12.3	...	..	.....	..	....	Rickets; bronchitis; hypertrophied adenoids and tonsils; diphtheria; complications; no improvement
97.	A. F.	2½	♂	1/11/18	17.3	...	..	0.105	..	....	Rickets
98.	S. S.	3	♂	2/ 1/18	18.6	2.7	..	0.121	..	....	Rickets and measles; improvement
99.	H. D.	1½	♀	12/13/18	....	...	...	.....	..	....	Rickets; calcium, 8.4 mg.
100.	P. E.	2½	♀	10/16/17	14.5	2.2	...	0.117	..	....	Rickets
101.	C. G.	2	♀	10/26/17	18.0	2.4	..	0.117	..	....	Rickets; improvement
102.	R. H.	3	♀	10/26/17	12.0	2.9	...	0.132	..	....	Rickets; gonorrheal vaginitis; no improvement
103.	I. B.	4	♂	10/30/17	12.3	1.3	..	0.114	58	....	Little's disease; improvement
104.	S. M.	6	♂	10/30/17	14.5	1.1	...	0.126	48	....	Bronchopneumonia; cure
105.	M. A.	7	♀	12/ 4/17	....	...	...	.....	51	....	Bronchial asthma; improvement
106.	W. F.	4¼	♀	10/25/17	14.0	2.4	...	0.126	..		
107.	R. W.	1/6	♀	10/30/17	13.0	2.4	...	0.117	..	....	Eczema; vaginitis; improvement
108.	A. P.	3	♂	10/12/17	15.6	...	..	0.09	..	....	Impetiginous eczema; cure
109.	C. J.	2½	♂	10/23/17	14.1	2.4	...	0.144	..	....	Eczema; improvement
110.	L. C.	12	♂	10/23/17	13.0	2.1	...	0.120	..	....	Impetiginous eczema
111.	F. L.	13	♀	12/ 5/16	11.6	1.2	...	0.114	..	52	Acute myositis; cure
112.	I. W.	13	♀	12/ 7/17	16.7	2.2	...	0.126	..	59	Hodgkin's disease; improvement
				1/18/18	15.1	2.5	..	0.140			
113.	M. L.	8½	♂	1/ 9/17	13.8	1.7	..	0.117	..	....	Purpura hemorrhagica; chronic hypertrophied adenoids and tonsils, operation; improvement and cure
114.	M. S.	12	♂	9/25/17	16.5	2.7	...	0.168	..	71	Purpura simplex; improvement
115.	S. S.	10	♀	2/20/17	11.6	1.9	5.0	0.160	..	....	Hypertrophied adenoids and tonsils; operation; cure
116.	L. L.	8	♂	10/30/17	12.6	2.1	...	0.108	..	58	Tonsillitis and fecal impaction; improvement
117.	H. K.	10	♂	7/13/17	12.6	3.2	...	0.135	..	....	Spastic colitis; improvement
118.	A. W.	10	♀	8/11/17	12.3	2.6	...	0.117	..	65	Chronic arthritis; improvement
119.	A. V.	12	♀	9/ 7/17	10.5	3.0	...	0.108	..	57	Duodenal ulcer; cure
120.	L. M.	11	♀	12/ 4/17	14.1	2.5	...	0.092	..	40	Duodenal ulcer; improvement
121.	W. D.	4/12	♂	10/12/17	11.1	...	...	.....	53	....	Pyloric stenosis; death
122.	P. P.	5	♂	12/28/17	16.1	2.4	...	0.093	..	....	Pyelitis and cervical adenitis
123.	S. K.	2	♀	10/16/17	14.1	2.4	...	0.099	..	....	Pyelitis; cholesterol 0.169 per cent.
124.	H. S.	7	♀	10/24/16	17.0	1.4	...	0.171	..	29-52	Pyelitis; hypertrophied adenoids and tonsils; cure
				10/28/16	11.6	1.0	...	.....	..	60	
125.	C. L.	6½	♀	5/ 7/18	17.2	3.3	...	0.077	..	....	Bronchopneumonia and congenital lues; death
126.	S. M.	3	♂	11/16/17	14.1	...	...	.....	..	....	Bronchopneumonia; cure
127.	L. W.	6	♂	11/19/17	14.5	1.1	...	0.126	..	....	Bronchopneumonia; cure
128.	A. Y.	6½	♀	6/13/18	11.6	...	...	.....	..	....	Bronchopneumonia and congenital syphilis
129.	G. P.	8½	♀	9/29/16	11.0	2.5	...	0.116	..	....	Incipient pulmonary tuberculosis; improvement
130.	J. L.	13	♀	.....	15.5	2.7	...	0.123	..	....	Pulmonary tuberculosis
131.	R. R.	11/12	♂	4/13/17	....	...	...	0.123	..	....	Miliary tuberculosis; PH 7.6; death
				4/17/17	....	...	...	0.111			

* In this column ♂ indicates male, ♀ female

TABLE 9.—Observations on Miscellaneous Conditions in Children—(*Continued*)

Case	Age, Years	Sex*	Date	Blood Analyses					Phenolsulphonephthalein, 2 Hour Output, per Cent.	Diagnosis; Outcome
				Urea N, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Sugar, per Cent.	CO_2 Combining Power, C.c. to 100		
132. R. C.	7	♀	1/ 7/18	14.6	3.0	...	0.135	..	....	Pleurisy with effusion; improvement
133. L. S.	11	♂	10/24/16	13.5	2.3	5.3	0.108	..	....	Cerebral sclerosis; improvement
134. M. W.	10	♀	10/26/16	11.0	1.6	...	0.126	..	....	Chronic bronchitis and bronchiectasis; improvement
135. M. M.	7	♀	12/ 4/17	....	...	...	.....	53	....	Chronic bronchitis; no improvement
136. D. F.	9	♂	11/ 9/16	11.0	2.4	...	0.162	..	....	Acute empyema; death
137. F. A.	8	♀	7/ 3/16	13.0	2.4	...	0.23	34	....	Paralysis followed by contractures; cure
138. B. L.	13	♀	9/26/16	12.0	1.8	...	0.111	..	50	Congenital syphilis; improvement
139. J. V.	3/12	♂	1/12/17	13.5	2.1	...	0.108	43	....	Congenital syphilis; improvement
140. S. B.	10	♂	8/15/16	13.0	1.8	...	0.132	..	....	Chronic endocarditis; improvement
141. S. S.	12	♂	9/22/16	14.0	1.0	...	0.12	..	62	Chronic endocarditis and myocarditis; improvement
142. M. F.	11	♀	11/30/17	13.0	1.3	...	0.126	..	72	Mild subacute endocarditis; improvement
			12/ 4/17	12.6	2.5	...	0.099			
143. S. B.	11	♀	12/ 4/17	11.2	1.8	...	0.132	..	47	Endocarditis; decompensated heart; no improvement
144. J. F.	13	♀	12/11/17	....	...	...	.....	..	73	Endocarditis; mitral stenosis; improvement
145. H. N.	8	♂	1/ 2/18	18.0	2.2	...	0.109	..	75	Septic endocarditis; secondary anemia; no improvement
146. R. F.	15	♀	9/21/15	18.0	2.5	7.2	0.09	..	59	Chronic endocarditis; aortic and mitral regurgitation; improvement
147. L. P.	14	♂	6/30/15	13.0	2.0	4.5	0.126	..	54	Chronic endocarditis; malnutrition; improvement
148. J. C.	9	♂	4/13/17	14.8	1.3	...	0.117	..	53 and 30	Chronic endocarditis and myocarditis; decompensation; casts and albumin; improvement
149. E. C.	10/12	♀	10/19/17	19.6	1.8	...	0.046	..	....	Decompensation; cholesterol 0.145 per cent; improvement

CONCLUSIONS

Chemical blood observations are reported on 149 children, thirty-eight of whom were nephritics and six diabetics. In general, the results obtained are quite similar to those obtained in the adult, although the kidney of the child would appear to act somewhat more efficiently than in the adult, resulting in slightly lower normal figures for the sugar, urea, creatinin and uric acid, and a slightly better phenolsulphonephthalein output.

In harmony with this, nephritis in children does not so quickly result in urea retention as in the adult, making the prognosis more favorable in early than in later life. As might be expected, creatinin retention rarely occurs in children, being found in four of our patients, two of whom died with symptoms typical of interstitial nephritis. We regard the blood urea as an especially helpful prognostic test in the nephritis occurring in children. The results of phenolsulphonephthalein tests harmonize very well with the clinical findings and the blood urea.

The carbon dioxid combining power of the blood is a very reliable method of ascertaining the severity of the acidosis in the diarrheal acidoses.

The reported blood findings of six diabetic children do not differ from similar observations in adults.

QUALITATIVE AND QUANTITATIVE CHANGES IN THE CEREBROSPINAL FLUID OF VARIOUS DISEASES AND THEIR SIGNIFICANCE *

A. LEVINSON
CHICAGO

The work discussed in this paper was undertaken with the view of determining, first, whether there are any chemical and physicochemical changes in the cerebrospinal fluid of meningism in addition to the physical changes very apparent in every case; and second, whether the chemical and physicochemical changes noted in the cerebrospinal fluid of meningitis, differ chemically and physicochemically only quantitatively or qualitatively as well in the various forms of the disease. In this study particular attention was paid to the question of acidosis—to which a great deal of prominence was given by Kopetzky,[1] who holds that "the predominance of the pressure symptoms as found in meningitis is in large measure due to a state of edema of the cerebral and meningeal tissues, and the edema is, in turn, the result of an acidosis evidenced clinically by the varying degree of acidity found in the cerebrospinal fluid." According to this theory, there would not only be no difference in the pathogenesis of the various forms of meningitis, but there would be no distinction between meningism and meningitis, or any other condition accompanied by an increased amount of cerebrospinal fluid which is in itself an evidence of intracranial pressure. Kopetzky's theory would make any one of these conditions the result of an acidosis.

My study comprised 155 cases that presented some form of meningeal involvement. Of this number 100 specimens of fluid were obtained from cases of meningism, that is, cases in which there was rigidity of the neck, a positive Kernig and Babinsky, but in which the meningeal symptoms soon subsided and an infection in some other part of the body made its appearance. Fifty-five fluids were obtained from various forms of meningitis, the greatest number coming from cases of meningococcic and tuberculous meningitis. In all of the fluids, the amount, the pressure, the number of cells and the various tests for globulin increase were noted. In addition to the above routine examination the fluids were also studied for the H ion concentration, the alkaline reserve, the chlorid, the amount of lactic acid, and the presence

---

* Read before the Section on Diseases of Children at the Seventieth Annual Meeting of the American Medical Association, June, 1919.

1. Kopetzky: Meningitis, Nature, Cause, Diagnosis and Principles of Surgical Relief, Manhattan Eye, Ear and Throat Hosp. Rep., **14**:15, 1913.

or absence of acetone bodies. The H ion concentration was determined by the same methods I had used in the study of my first series,[2] namely, the gas chain and the Levy-Rowntree-Mariott indicator method.[3] The alkaline reserve of the fluid was determined both by the Van Slyke carbon dioxid[4] method and by titration with methyl red as an indicator.[5] The chlorid was determined by the Seelman method,[6] the lactic acid was roughly determined by the Uffelmann reagent originally described for urine examination with the slight modification of counting of the number of drops of cerebrospinal fluid necessary to turn 5 c.c. of the reagent to a canary yellow; acetone was determined qualitatively by the sodium nitroprussid method used for urine.

Of the 100 cases of meningism under observation, all showed an increase in the amount and pressure of the cerebrospinal fluid. The amount of fluid removed at one sitting varied between 15 and 40 c.c., compared to 10 c.c., which is the maximum amount I was ever able to remove in one sitting in normal cases, or cases that present no signs of meningeal irritation. The pressure varied between 200 and 700 mm. of water compared to 90 mm. of water in normal cases, with the patient in the recumbent position. No sediment was found in any of the fluids. In eighty-five cases the cells numbered less than 6 per cent.; in fifteen cases they were increased in number. The same was true of the globulin content, only fifteen of the 100 cases showing an increase in globulin. The chlorids ranged between 0.6 and 0.74 gm. per 100 c.c. of fluid, which is the average range for normal fluid as well. Lactic acid was present in the same amount as in normal fluid, requiring from 15 to 20 drops of cerebrospinal fluid to turn 5 c.c. of Uffelman's reagent to a canary yellow. Acetone bodies were negative in all of the fluids. The H ion concentration ranged between 7.4 and 7.6 in terms of p_H when the fluid was examined immediately after withdrawal from the body. On standing, however, the H ion concentration of the fluid changed rapidly toward the alkaline side, reaching a p_H of 8.1 or 8.3 in from five to twelve hours, after removal from the body. The alkaline reserve ranged between 36 to 63 per cent. of carbon dioxid bound by the cerebrospinal fluid at 760 mm. barometric pressure and zero

2. Levinson: The Hydrogen Ion Concentration of Cerebrospinal Fluid. J. Infec. Dis. **21**:556 (Dec.) 1917.

3. Levy, Rowntree, Marriott. A Simple Method for Determining Variations in the Hydrogen-ion Concentration of the Blood, Arch. Int. Med. **16**:389 (March) 1915.

4. Van Slyke: A Method for Determination of Carbon Dioxid and Carbonates in Solution, J. Biol. Chem. **30**:347 (June) 1917.

5. Levinson: Studies in Spinal Fluid, Arch. Pediat. **33**:241, 247 (April) 1916.

6. Seelman: Simple Test for Estimating Chlorides in the Urine Founded on Volhard's Method, J. Lab. & Clin. Med. **1**:444 (March) 1916.

temperature, the greatest number varying between 45.7 and 63 per cent., the same as in fluid that presented no signs of meningeal irritation.

From the above findings, I believe I am justified in concluding that only a small percentage of fluids from cases of meningism show any chemical changes (increase in globulin) and that no fluid from cases of meningism shows any physicochemical changes. This is especially true in regard to the H ion concentration and the alkaline reserve of the fluid of meningism, both of which were found to be the same as in the fluid of normal cases. Acidosis, therefore, does not account for the production of meningism.

The fifty-five fluids withdrawn from cases of meningitis showed several marked differences between the various meningitides. Not only was there a difference between the colorless fluid of tuberculous meningitis and the turbid fluid of suppurative meningitis, but there was even a difference in the shades of turbidity between the fluids of various meningitides. The fluid of pneumococcus meningitis had, as a rule, a pearly-gray color, while that of meningococcus meningitis had a yellowsh green tinge that at times turned entirely green when the fluid was allowed to stand for any length of time. The action of chemicals on the turbidity is interesting. All meningococcic fluids cleared up on the addition of from 0.1 to 1.5 c.c. of hundredth normal sodium hydroxid, and all fluids of tuberculous meningitis were precipitated by the addition of from 0.1 to 1.5 c.c. of hundredth normal sulphuric acid.

The sediment, which is present in all forms of meningitis, also differed in form in different types of meningitis. The sediment in cases of tuberculous meningitis appeared as a white fibrinous structure suspended from the center, and that of meningococcus meningitis as a balloonlike mucoid mass that changed with various stages of the disease. The pneumococcus sediment sunk to the bottom of the test tube early in the disease.

As to the protein in the cerebrospinal fluid of various meningitides, the matter of quantity was of minor importance compared with the quality of the protein.

It is true that in most cases of suppurative meningitides there is a larger amount of protein in the cerebrospinal fluid than in most cases of tuberculous meningitis. It is also true, however, that it is not the quantity that is the most important factor, but it is the quality or the electrical charge of the protein. Tashiro and I[7] have shown that fluid

7. Tashiro and Levinson: Alkaloidal and Metallic Precipitation of Cerebrospinal Fluid in the Diagnosis of Meningitis, J. Infec. Dis. **21**:571 (Dec.) 1917.

from cases of meningococcus meningitis moves toward the cathode in the cataphoresis tube, thus showing that the fluid is electropositive, and that the fluid from cases of tuberculous meningitis moves toward the anode showing that the protein in that case is electronegative. This has been further demonstrated by adding 1 c.c. of cerebrospinal fluid to 1 c.c. of a 3 per cent. sulphosalicylic acid solution in one tube, and 1 c.c. of cerebrospinal fluid to 1 per cent. mercuric chlorid solution in another tube. This is allowed to stand for twenty-four hours and the sediment measured. The fluid in cases of tuberculous meningitis gives the greatest precipitation with the mercuric chlorid solution and the fluid of cases of meningococcus meningitis gives the greatest precipitation with the sulphosalicylic acid solution. These differences held true in the present series of cases as well. Of the other chemical differences between the various forms of meningitis should be mentioned the differences in the chlorids. In the series of fifty-five cases the chlorids in the fluids of all cases of suppurative meningitides were normal or slightly less than normal in amount, varying between 0.6 to 0.74 gm. per 100 c.c. On the other hand, the fluids of cases of tuberculous meningitis were found below normal, falling to as low as 0.5 gm. per 100 c.c.

The physicochemical findings were also different in the various types of meningitis. The colloidal gold chlorid test in cases of tuberculous meningitis gave the greatest discoloration in the fifth, sixth and seventh tube, and all cases of suppurative meningitis in the eighth and ninth tubes. As to the H ion concentration of various meningitides: The fluid in cases of meningococcus meningitis varied between a p_H of 7.2 to 7.4 immediately after removal from the body and that of cases of tuberculous meningitis between 7.4 to 7.6, the same as in normal fluid. The difference was still more marked when the fluid had been standing, the fluid of meningococcus meningitis retaining the same reaction and of tuberculous meningitis becoming more alkaline. The alkaline reserve in cases of meningococcus meningitis varied between 18 and 35 per cent. of carbon dioxid bound by 100 c.c. of cerebrospinal fluid at zero temperature and 760 degrees barometric pressure, and fluid from cases of tuberculous meningitis had an alkaline reserve only slightly below normal.

It is evident, then, that there is a difference in the fluid in the various forms of meningitis, and that there is an increased H ion concentration only in some types of meningitis, namely, in the cases of suppurative meningitis, but not in tuberculous cases. This, I believe, would exclude the generalization of acidosis.

Further proof of the fallacy of generalizing all changes in cerebrospinal fluid is found in a study of the cerebrospinal fluid in systemic or

metabolic diseases. It has been found by me as well as by other observers that whenever there is retention of chemical substances in the blood, there is an increase of the same chemicals in the cerebrospinal fluid. In nephritis, for instance, where there is a retention of chlorids in the blood, there is a corresponding increase in the amount of chlorids in the cerebrospinal fluid, reaching in some of my cases as high as 0.85 gm. per 100 c.c. compared with from 0.60 to 0.74 gm. per 100 c.c. in the normal. In uremia, where there is a retention of urea in the blood, the same phenomenon is noted in the cerebrospinal fluid, and in diabetes, where the blood sugar is increased in amount, there is also an increased sugar content in the cerebrospinal fluid, reaching in one of the cases as high as 0.3 per cent. The reaction of the fluid remains the same; the colloidal gold chlorid test, as well as the other tests, are negative.

The characteristic gold chlorid curves in tabes and general paresis further show that there is something fundamentally different between the various diseases and even in the fluid of various forms of the same disease, such as syphilis of the central nervous system.

I believe it is no more possible to generalize all changes in cerebrospinal fluid, be it on a basis of acidosis, or any other basis, than it is to generalize all diseases of the chest cavity, or all diseases of the peritoneal cavity.

The pathogenesis of meningism, I believe, must be looked for and explained on simple mechanical grounds. If one keeps in mind that the cerebrospinal fluid is greatly influenced by the blood pressure inside of the cranium, it can easily be seen that any irritation reaching the brain either by general circulation, as in pneumonia, for instance, or through adjacent structures, such as in otitis media, will accelerate the circulation of the blood in the cranium, thus raising the cranial blood pressure and therefore also producing an increase in the cerebrospinal fluid pressure. Whether there is only an increase in the pressure of the cerebrospinal fluid which is released from the subdural space on doing a lumbar puncture, or whether there is an actual increase in the production of the fluid cannot be stated with certainty as long as the mode of origin of cerebrospinal fluid is not known. However, using pleural fluid in pneumonia as an analogy, it is plausible to assume that there is an actual increase of the fluid in meningism.

It is my experience, and surely is the experience of other men, that in some cases of pneumonia there is an increase in the fluid of the pleural cavity. This increase, however, does not always mean an empyema or a pleurisy. The fluid, which is serous in character and sterile, often becomes absorbed with the subsidence of the pneumonia. This, most likely, also takes place in cases of meningeal irritation,

namely, an increase in the production of the cerebrospinal fluid, and a resulting increase in pressure. However, whether there is an actual increase in amount, or only an increase in pressure, I believe it is certain that the main factor in the production of meningism is the increase in the blood pressure in the cranial cavity, which in turn gives rise to an increase in the cerebrospinal fluid pressure on purely mechanical grounds.

Because there is no change in the reaction of the fluid, and only an occasional change in the chemical composition of the fluid, the meningeal symptoms subside immediately after the withdrawal of the extra quantity of the fluid in the subdural cavity or as soon as the principal disease in some other part of the body develops; for instance, I have noticed often that as soon as the pneumonia is fully developed the meningeal symptoms disappear. This, I believe, can be explained by the assumption that as soon as the pneumonia is fully developed the large volume of blood is removed from the brain and transferred to the lungs, thus decreasing the cranial blood pressure, and consequently decreasing the cerebrospinal fluid pressure.

That this is the case seems evident from the cases of meningism in which no spinal puncture has been done, and still the symptoms subside, the fluid in the subdural cavity being absorbed as soon as the volume of blood in the cranium is decreased.

Several terms have been used in the literature to denote conditions giving rise to meningeal symptoms and which show no symptoms of typical meningitis. Sevestre,[8] in 1890, reported the presence of meningeal symptoms in cases of grippe and called it grippal pseudomeningitis. Pissavy[9] spoke of three types of grippal meningitis, or rather meningeal symptoms accompanying grippe, (1) congestive, or cases in which the patient gets well easily; (2) serous, or cases with increased fluid; and (3) suppurative, or cases produced by suppurative organisms. Dupré,[10] in 1894, coined the word meningism, a term used to this day. It is interesting to note that although lumbar puncture was described by Quincke in 1891, Dupré does not mention lumbar puncture. The diagnosis of meningism, according to him, is to be made by the previous history, by the associated symptoms and by the urinary phosphates. With easy access to cerebrospinanl fluid our conception of meningism changed. Meningism, as we now understand the term, is applied to cases that show symptoms of meningeal irritation and in which the cerebrospinal fluid is sterile, containing only very

8. Sevestre: De la pseudo-meningite grippale, Bull. et mém. Soc. méd. d. hôp. de Par. **7**:261, 1890.
9. Pissavy: Complications, nerveuses de la grippe, Paris, 1903.
10. Dupré: Le meningisme, Congrès français de médecine, **1**:411, 1895.

few cells (from 4 to 6 per c.mm.), and showing no increase in the globulin content. In some of my cases the fluid showed an increase in the number of cells and in the globulin content and still they were cases of meningism clinically, as the meningeal symptoms disappeared after a lumbar puncture. Instead of meningism it probably would have been better to use a term showing the correlation between the meningeal condition and the original conditions, for instance, meningo-pneumonia or meningo-otitis. However, the original condition is not always easily determined and the combined term may give rise to confusion. I would, therefore, suggest to retain the term meningism.

Interesting in this connection is the fact that the condition known as meningism was originally described with the epidemic of influenza that swept over Europe in 1889-1890 and its recurrence in 1893 and 1894. Still, in the recent epidemic of influenza (1918) I did not see any cases of meningism accompanying influenza.[11]

The predisposing causes of meningism is another point of interest. Dupré and a number of other French observers considered worms, teething and hysteria as being the predisposing causes. I could see no relation between meningism and any of the three conditions in my cases. I do, however, believe that while the direct cause of meningism is the congestion of the brain by some infection, there is usually some predisposition in the infant toward meningeal and brain irritation, which cannot be measured by the electrical current, as in tetany, but which is, nevertheless, an unstability of the nervous system.

The pathogenesis of meningitis must be dealt with separately in each form, and while there is a common element between all forms of meningitis in that they are all produced by bacteria, the reaction of the meninges to the bacteria is different in each one of them; or at least different between that of suppurative meningitis and tuberculous meningitis. The same is true of the pathogenesis of meningitis as compared with that of meningism; while there is a common pathologic ground between meningitis and meningism in that the fluid is increased in both cases, the pathogenesis is different entirely, in that in meningism there is a pure mechanical disturbance which can be relieved either by withdrawing the cerebrospinal fluid by mechanical means or by the localization of the infection in another part of the body, thus lessening the blood in the cranium and thereby lessening the cerebrospinal fluid in the subdural cavity, while in meningitis there is a destruction of the tissue.

Do the above data and conception of the changes of cerebrospinal fluid in various diseases have a practical bearing on the diagnosis of

---

11. Levinson: Clinical Observations on Influenza with Special Reference to Blood and and Blood Pressure, J. Infec. Dis. **25**:1 (July) 1919.

conditions involving the meninges? I believe that in diagnosis the absence of sediment in nonmeningitic fluid, the presence of sediment in all forms of meningitis, and the difference in the sediment of the fluid in the various types of meningitis are valuable findings; likewise are the behavior of the fluid in the cataphoresis tube; the behavior of the fluid toward alkaloid and metallic precipitants, such as sulphosalicylic and mercuric chlorid, the changes in the fluid by the addition of sodium hydroxid and sulphuric acid, the alkaline reserve and the colloidal gold chlorid test. These changes have been found to be of practical help, not only in differentiating meningism from meningitis, but also in differentiating the type of meningitis, although it goes without saying that the final diagnosis must rest on the demonstration of the specific bacteria in the fluid.

In addition to the above, the amount of chlorid, urea and sugar in the fluid will help to diagnose certain systemic conditions where there is no involvement of the meninges.

CONCLUSIONS

From the above data, I believe I am justified in drawing the following conclusions:

1. The changes in cerebrospinal fluid in various diseases cannot be generalized, each disease presenting at least some changes peculiar to itself.

2. Classification of cerebrospinal fluid changes must take into consideration qualitative as well as quantitative changes.

3. There are three types of conditions that produce changes in the cerebrospinal fluid: meningism, meningitis and systemic disturbances.

4. The meningismal changes manifest themselves in an increase in pressure and amount of the fluid. Occasionally, there are also cytologic and chemical changes.

5. There is no evidence of acidosis in the cerebrospinal fluid of meningism.

6. The mode of production of meningism is mechanical, being due to an increase in blood pressure in the cranium.

7. Changes in the cerebrospinal fluid of various forms of meningitis differ from each other not only bacteriologically and cytologically, but also physically, chemically and physicochemically.

8. The cytologic, chemical and physicochemical differences in the various forms of meningitis are both quantitative and qualitative.

9. The H-ion concentration of the fluid of suppurative meningitis is often increased.

10. The H-ion concentration of the fluid of tuberculous meningitis runs parallel with that of normal fluid.

11. One of the indications of the presence of a meningitic process as distinguished from the meningism is the presence of sediment in the fluid.

12. The systemic changes in cerebrospinal fluid are encountered during the course of metabolic diseases and manifest themselves in an increase of certain chemical constituents in the fluid, such as chlorids in nephritis and sugar in diabetes.

13. The various types of changes in the cerebrospinal fluids can be used for the diagnosis of various diseases.

14. A useful diagnostic means for the differentiation between various types of meningitis is the behavior of the fluid toward various precipitants such as alkaloidal and metallic precipitants.

A RÉSUMÉ OF SOME EXPERIMENTAL STUDIES ON CUTANEOUS HYPERSENSITIVENESS*

E. C. FLEISCHNER, K. F. MEYER
AND
E. B. SHAW
SAN FRANCISCO

About ten years have passed since Mantoux and Moussu[1] in France, and Mendel[2] in Germany, first called attention to the value of the intradermal method of eliciting cutaneous hypersensitiveness, although in 1903 Mendel established the fact that, if in giving tuberculin intravenously a portion went into the tissues around the vein, a severe reaction took place in infected individuals. Antedating these observations by several years, however, Escherich described a local reaction following the subcutaneous injection of tuberculin, which he called "stich reaktion," and in 1905, von Pirquet[3] published his epoch making observations on cutaneous hypersensitiveness, to which he applied the term "allergy." Since these publications, it is, indeed, striking to note the paucity of investigators that have interested themselves in this fascinating problem. A fairly large number of men has drawn clinical deductions on the relative value of the intradermal test, as compared with the von Pirquet reaction, but work tending to explain the cause or the meaning of cutaneous hypersensitiveness has been conspicuously rare. Furthermore, it is singularly striking that whereas the original experimenters based their results entirely on findings in animals and humans suffering from tuberculosis, it has not stimulated others to study the question in relation to other diseases.

In Europe Römer[4] investigated the cutaneous tuberculin reaction most intensively, and in this country, Baldwin[5] and later Krause[6] studied the subject, particularly in experimental animals, drawing from their work many valuable conclusions. In an effort to determine, if

---

* From the George Williams Hooper Foundation for Medical Research and the Pediatric Department of the University of California Medical School.

* Read at the Thirty-First Annual Meeting of the American Pediatric Society held in Atlantic City, June 16-18, 1919.

1. Mantoux, C., and Moussu, G.: Compt. rend. Acad. d. sc. **147**:502, 1908.
2. Mendel, F.: Med. Klin. **12**:402, 1908.
3. Von Pirquet: Handb. d. Technik & Methodik d. Immunitätsforschung, 1911, Suppl. 1, p. 191.
4. Römer, R. H., and Joseph, K.: Beitr. z. Klin. d. Tuberk. **14**:1, 1909.
5. Baldwin, E. R.: J. Nat. Assoc. Study & Prev. Tuberc., 7th Ann. Meeting, 1911, p. 351.

possible, the cause of cutaneous hypersensitiveness, Baldwin placed in the abdominal cavities of guinea-pigs, capsules of porous Berkefeld filter clay, some of which had been filled with living tubercle bacilli, and others with filtered watery extracts of bacilli, i. e., tuberculoprotein, and then sealed them with dental cement. Cutaneous hypersensitiveness was not present in tests made on the fifteenth and fifty-seventh day after the experiment. The capsules became encysted in a few weeks and Baldwin drew the conclusion that cutaneous hypersensitiveness did not develop through the mere presence of tubercle bacilli in the body, even though they were more or less accessible to the body fluids. Anaphylaxis was present in these animals. Believing that absorption from the capsules might be either too quick or not sufficiently prolonged, he used an emulsion of animal charcoal that had absorbed the bacillary extract, and injected it under the skin and into the peritoneal cavities of his animals. The results were likewise negative on the twenty-first, one hundred and sixth, one hundred and fifty-fifth and two hundred and sixth day. Conjecturing that cutaneous hypersensitiveness depended on some property inherent in the serum of tuberculous animals, he injected into the guinea-pigs which had received the charcoal emulsion of bacillary extracts, serum of diseased pigs before and at the time of the tests. His results were entirely negative.

Assuming the possibility that the fatty or waxy substances in the bacilli might have something to do with the development of positive tests, he injected small amounts of benzol extracts of tubercle bacilli intraperitoneally, and alcohol ether extracts subcutaneously and intraperitoneally into animals that had already received the protein in charcoal. Positive tests were conspicuously absent. He was not able to produce cutaneous hypersensitiveness by injecting either the whole blood or the serum of hypersensitive guinea-pigs. He was likewise unable to get positive tests when he used for testing an antigen made from the plasma of tuberculous livers, spleens, glands, old or new tubercles.

Baldwin therefore concludes that for positive cutaneous hypersensitiveness to be present, tubercle must exist in the body. These tubercles may come from the injection of dead sterilized bacilli, in which case the positive reactions are less persistent than in animals subject to living infection. He states further that the persistency and delicacy of the reaction appears to be associated with tubercles which are not wholly fibrous. It may be due to slow disintegration and digestion of the bacilli in the periphery of the caseated center. Baldwin adds that he can understand why such a reaction should occur in the focus of infection, because of changed cell functions

created to meet the need at the time and place, but how the distant cells in the skin can acquire these reacting functions, is less easily comprehended. His conclusion, therefore, seems warranted that in nature's method of extracting and disintegrating bacilli, some product is set free in the blood to act on the distant cell groups not connected with the tubercle, or in contact with the bacilli.

Following Baldwin's very valuable work, Krause[6] carried out a series of experiments having important bearing on the problem. He injected guinea-pigs with two well known strains of tubercle bacilli, one of which, H37, was very virulent, causing generalized tuberculosis, the other, R1, was very benign, with a tendency simply to involve regional lymph nodes, from which process the animals ultimately made a complete recovery. The group injected with H37, the virulent strain, showed increasing cutaneous hypersensitiveness from eleven days after the injection, when the first regional changes were noted, to the forty-sixth day, when the disease was well advanced. At every stage the reaction was more intense than in the R1 animals. In the group injected with the R1 strain, the reaction increased as the disease developed. After it came to a standstill and began to heal, the cutaneous hypersensitiveness became milder. The ability to react, however, never entirely disappeared.

Krause raises the question from this observation, as to whether an infection like tuberculosis, once it gains anatomic (not mere bacillary) foothold, is ever entirely wiped out. In the guinea-pigs injected with the R1 strain, he often found no tubercles macroscopically, but was able to demonstrate small ones microscopically, so that there is always the possibility that a tubercle, however small, may exist to give cutaneous hypersensitiveness.

To determine the effect of reinfection on the power to react cutaneously, Krause injected animals that were recovering from the R1 strain with the virulent organism, H37. Cutaneous hypersensitiveness rapidly increased. He also injected a set of guinea-pigs with acid fast Timothy bacilli, which produce a tumor going on to abscess formation from two to four days after inoculation, with regional lymph node enlargement. Seven days afterward he got positive skin tests, which had diminished very much on the twenty-second day. Twenty-five days after the original infection, the animals were again injected with Timothy bacilli. Three days later, twenty-eight days after the first injection, the skin tests were more pronounced than at any time, confirming the observations made with the tuberculous animals, that reinfection with an organism increases cutaneous hypersensitiveness.

6. Krause, A. K.: J. M. Res. **35**:1, 25, 43 (Sept.) 1916.

Timothy bacilli produce lesions in guinea-pigs very much more rapidly than tubercle bacilli, and corresponding to this, positive skin tests appear much earlier. Both lesions and hypersensitiveness, however, are more transitory in Timothy bacillus disease than in tuberculosis.

Krause injected a series of animals that had been infected with the virulent H37 organisms and had developed cutaneous hypersensitiveness, with tuberculin intraperitoneally. They became very sick, and during this period, the skin tests, which had been strongly positive, diminished very much in intensity. His conclusions are: 1. Cutaneous hypersensitiveness is never present without a focus. 2. It appears coincidental to the establishment of the focus. 3. It diminishes with the healing of the focus. 4. It varies with the virulence of the invader. 5. It is probably never entirely lost except in the presence of pregnancy or intercurrent disease. 6. It is increased by reinfection. 7. It is diminished or completely wiped out during a period of general tuberculin reaction. 8. The suggestion is offered that tissue hypersensitiveness may be a function of immunity to reinfection.

Gelien and Hamman,[7] who made a large number of observations on cutaneous hypersensitiveness in humans, conclude that, since nearly all adults are infected with tubercle bacilli, one may assume that a low grade of tuberculin hypersensitiveness is constantly present. With a fresh invasion, either from within or without, this increases. If the disease subsides and the individual recovers, the hypersensitiveness falls to a lower or the original level. If the tuberculosis remains active, the high level of the hypersensitiveness persists and lasts until the body is overwhelmed and the resistance broken entirely down by the disease, at which time all evidence of cutaneous hypersensitiveness ceases.

It is apparent, therefore, that these investigators explain cutaneous hypersensitiveness on the assumption that it is always an evidence of infection, and their experiments are ample proof of their contention.

During the past three years we have made an intensive study of cutaneous hypersensitiveness in connection with several problems that entailed the infection of a large number of guinea-pigs. In 1916, certified milk was studied in an effort to determine the presence of tubercle bacilli, and incidently an enormous number of animals developed the lesions produced by the *B. abortus bovinus*. In the diagnosis of these infections, no test was so constantly positive as the intradermal skin test. During the same period, many guinea-pigs were infected with tuberculous material from various sources, and positive intradermal reactions were always and only present in the diseased

7. Gelien, T., and Hamman, L.: Bull. Johns Hopkins Hosp. **28**:163 (May) 1917.

pigs, so that the conclusion was drawn that in guinea-pigs which are infected with *B. abortus bovinus* or *B. tuberculosis,* positive cutaneous hypersensitiveness is always an indication of infection.

During 1917, the problem was attacked from another angle. It seemed highly desirable, after contending that positive cutaneous hypersensitiveness was always an evidence of infection in guinea-pigs, to immunize a series of animals by the repeated injection of antigens derived from the organisms with which the preceding guinea-pigs had been infected, and to study the skin reactions in these immunized pigs. Gay and his co-workers[8] had previously claimed that positive skin tests were an evidence of immunity, drawing their deductions from work with typhoidin. Nichols[9] had questioned this conclusion (?), however, because he obtained similar typhoidin reaction in soldiers who had been vaccinated with paratyphoid, and it is well known that paratyphoid vaccination will not immunize against typhoid. He considered the reaction an evidence of previous protein sensitization. Austrian,[10] Kolmer[11] and many others likewise failed to get results whereby the work of Gay and his pupils could be authenticated. Meyer and Christiansen[12] failed to confirm the observations of Gay by conducting a very searching inquiry into the mechanism of cutaneous hypersensitiveness in the rabbit. A positive typhoidin reaction in a rabbit never indicated, according to their observations, that this animal will resist a subsequent intravenous injection of living typhoid bacilli, or that the animal is so protected that it will not become a chronic carrier of bacilli in its gall-bladder or liver. Unpublished experiments with other organisms than the typhoid bacillus confirmed these conclusions, and also convinced these workers that the rabbit is a most unsatisfactory animal for the study of cutaneous hypersensitiveness.

Bearing this rather conflicting literature in mind, guinea-pigs were immunized by repeated intraperitoneal injections of the following antigens: dead *B. abortus bovinus,* dead *B. typhosus,* old tuberculin, bovine, *B. abortus protein.* That a high grade of immunization was established in all of these animals was evidenced by the constantly positive agglutination reactions. The antibody content of the blood must have been very great, because the tests were distinct in dilutions as high as 1:2,000 in the pigs that had been injected with all of the antigens except the tuberculin. Complement fixation tests on the

8. Gay, F. P.: Arch. Int. Med. **13**:471 (May) 1914; **14**:671 (Nov.) 1914.
9. Nichols, H. J.: J. Exper. M. **22**:78, 1915.
10. Austrian, C. R., and Bloomfield, A. L.: Arch. Int. Med. **17**:663 (May) 1916.
11. Kolmer, J. A., and Berge, Jr., J. H.: J. Immunol. **1**:409 (Aug.) 1916.
12. Meyer, K. F., and Christiansen, C. R.: J. Infect. Dis. **20**:357, 391 and 424 (April) 1917.

serum of these pigs, using the tubercle bacillus as an antigen, were unsatisfactory, which corresponds to the experience of many investigators on complement fixation in tuberculosis. Intradermal tests were made on all of these animals, and in no single instance was a positive one obtained. Postmortem examinations failed to reveal any evidence of infection.

Not content with drawing a conclusion from this set of experiments, another series of animals was injected with the same antigens, using much larger dosage. Besides repeating the above mentioned injections, one set of ten pigs was injected with dead rodent *B. paratyphosus,* that was known to be very virulent for guinea-pigs. Agglutination tests were constantly positive, cutaneous hypersensitiveness was always negative and necropsies failed to show the presence of the slightest lesion in any animal. It seemed, therefore, justifiable to state that while in guinea-pigs, cutaneous hypersensitiveness was always a sign of infection, a high state of developed immunity without infection evidenced by a pronounced antibody content of the blood, giving positive agglutination reactions in high dilutions, never produced cutaneous hypersensitiveness. Stated simply, in guinea-pigs cutaneous hypersensitiveness is always a sign of infection and never a sign of immunity.

These experiments establish for the guinea-pigs a definite biologic law. Conditions which will sensitize an animal in an anaphylactic sense, will not necessarily sensitize its skin, and that to bring about cutaneous hypersensitiveness, certain very definite and strict requirements must be fulfilled. In no other way than by the introduction of bacilli and the consequent production of foci has anybody thus far succeeded in sensitizing a guinea-pig's skin. The mere injection of protein, soluble or insoluble, will not produce skin sensitiveness, but will render the animal anaphylactically sensitive.

During the past year, this work has been continued, using a variety of infecting organisms for confirmation of previous results. Furthermore, it seemed essential to study the problem from other angles. Baldwin, in his work, had made the statement that anaphylaxis was present in his animals, although he did not obtain positive skin tests in the absence of infection. He did not elaborate, however, on the possible connection of these phenomena. Some observers, particularly Kolmer,[13] having contended that hypersensitiveness was an indication of the anaphylactic state, as it affected the skin, the importance of studying the relationship of cutaneous hypersensitiveness to anaphylaxis naturally suggested itself. Having demonstrated that animals that had been injected with dead organisms developed high antibody content in their blood, but never showed positive intradermal reactions,

13. Kolmer, J. A.: Bull. Johns Hopkins Hosp. **28**:163 (May) 1917.

it seemed logical to study also the effect of inoculating these pigs later with living bacteria, and observing the result of this subsequent infection on the cutaneous hypersensitiveness.

While this work was in progress, Evans[14] published her very illuminating article, in which she showed that morphologically, serologically and biochemically the *B. abortus bovinus* and the organism which causes undulant or Malta fever, were practically indistinguishable. Her attention was first called to the problem by the observation made in this country that practically all raw cow's milk contained *B. abortus,* and the work of the British Commission, which showed that the milk of 41 per cent. of the goats in Malta contained *B. melitensis.* In her work, Evans used strains of *B. abortus* that were agglutinated by an abortus immune cow's serum in dilution of 1:1,280 or higher. She used six strains of *B. melitensis,* the history of five of which is as follows: (1) *B. melitensis* (Dr. Annett) was obtained from England in 1907; (2) *B. melitensis,* stock 22; (3) *B. melitensis,* stock, received from the Pasteur Institute in Paris prior to 1900; (4) *B. melitensis,* R. A. M. C., obtained from the Royal Army Medical College of London, England, in January, 1908; (5) *B. melitensis,* U. S. Navy, obtained from the U. S. Naval Medical School in March, 1909. These five strains responded alike to cultural, biochemical and serologic tests. Comparison of the *B. abortus* and the *B. melitensis* showed them to be identical as far as growth on the various culture media was concerned for the first seven days. After that, the *B. melitensis* growth was a little browner. The biochemical changes of the two organisms were the same, and the agglutination reactions to a *B. abortus antiserum* were exactly alike.

A series of animal experiments was carried out as follows: Four pregnant guinea-pigs were infected with *B. abortus* and four with *B. melitensis,* the method of inoculation not being stated. In a few days, three animals in each group aborted, and five days after the inoculation, one animal was killed from each set. In from three to four days, characteristic dew drop colonies made their appearance on both sets of slopes inoculated from the liver, spleen and uterus of the infected animal. Several weeks later, the *B. melitensis* slopes showed a more intense brownish coloring. No other difference was distinguishable. Thirteen days after the inoculation, serum was obtained for agglutination tests. The results with the guinea-pig *B. abortus* antiserum were the same as with the cow's antiserum. With the guinea-pig *B. melitensis* antiserum, however, the results were less uniform. *B. abortus* strains were agglutinated in dilutions of 1:320

14. Evans, A.: J. Infect. Dis. **22**:580 (June) 1918.

and 1:640. Two of the *B. melitensis* strains were agglutinated in dilutions of 1:1,280, one 1:2,560, and the homologous strain in a dilution of 1:5,120.

Evans carried out an interesting set of absorption tests. For practical purposes using a *B. abortus* antiserum, this method cannot distinguish *B. abortus* from *B. melitensis*. Using a *B. melitensis* antiserum, the results are not quite the same. The melitensis antiserum acts on the melitensis antigen the same as the abortus antiserum acts on both. The melitensis antiserum acts on the abortus antigen the same as the abortus antiserum, except in characteristic lower dilutions. The melitensis serum with the melitensis antigen absorbs all the agglutinins, which are active toward *B. abortus*. Melitensis antiserum, after acting on *B. abortus*, acts in the same way on the melitensis antigen as it would have acted without being saturated. Evans explains these absorption tests by assuming that both the abortus and melitensis antiserums are alike in kind, but differ in proportion, and that the corresponding agglutinable substances are present in the bodies of the two species of bacteria in different proportions. One can only distinguish the two organisms by a *B. melitensis* antiserum, when the agglutinating strength of the serum for both species is known. Judging from these experiments, agglutination tests which have been relied on for the diagnosis of undulant fever have not proved whether the infections were due to *B. melitensis* or *B. abortus*.

In connection with a discussion of these absorption tests, it may be said that this method was used by Nègre and Raynaud[15] to distinguish *B. melitensis* from *B. paramelitensis* (the original strain of Bruce) based on the assumption that similar reactions had been considered sufficiently distinctive to separate *B. dysentericus* from *B. paradysentericus*, and the meningococcus from the parameningococcus. If their contentions are correct, Evans' work suggests that *B. melitensis* and *B. abortus* are more closely related than *B. melitensis* and *B. paramelitensis*. Incidently, without at this time further elaborating on the possible pathogenicity for man of the *B. abortus*, one might call attention to a case of paramelitensis fever reported by Basset-Smith[16] in which the patient had all the clinical signs of undulant fever for two years, but never gave positive serologic reactions until the *B. paramelitensis* was used as antigen, when the tests were positive in high dilutions.

Evans' results suggested two very fascinating possibilities, both of tremendous scientific interests and one of possible serious import. The first possibility was that in the *B. melitensis*, another organism,

15. Nègre, L., and Raynaud: Compt. rend. Soc. de biol. **72**:664, 791, 1912.
16. Basset-Smith, P. W.: J. Roy. Naval Med. Serv. **1**:166, 1915.

very intimately related to the *B. abortus bovinus* was obtainable, that was pathogenic for guinea-pigs, and might offer a very fertile field for the further study of cutaneous hypersensitiveness. The second possibility entailed a careful investigation of the pathogenicity for man of the *B. abortus bovinus,* considering its very great serological, biochemical and cultural similarity to the *B. melitensis,* the recognized and accepted etiologic agent in undulant fever. It is with the first of these problems, only, that part of this paper has to deal.

A careful résumé of the literature, with reference to guinea-pig inoculation with *B. melitensis,* showed a relatively small number of observations. Durham,[17] in 1898, injected guinea-pigs intracerebrally with cultures whose virulence had been increased by previous intracerebral inoculations, a method which had originally been used to raise the virulence of *B. influenzae.* In animals that died the organism was recovered from the viscera. Not much is given as to his postmortem findings. In guinea-pigs that died at remote periods, the kidneys were intensely engorged, and in two instances the spleen was much enlarged, the other organs showing nothing abnormal. Following the intraperitoneal injections, the results were much more chronic in character.

In 1904, Carbone,[8] who later died of undulant fever contracted in his laboratory, showed that male guinea-pigs often developed a purulent inflammation of the tunica vaginalis, following the intraperitoneal injection of *B. melitensis.* It is to Eyre,[19] however, that most credit is due for having studied the *B. melitensis* in relation to guinea-pig infections. He showed that following the first isolation from human cases the *B. melitensis* could only kill guinea-pigs when given subcutaneously, intravenously or intraperitoneally in tremendous doses. Infection was also possible by intracranial inoculation. Using a freshly isolated strain, the infection was very chronic, the animals living from one to two hundred days. By repeated intracranial injections, he was able to increase the virulence of the organisms so that the pigs died within twenty-four to seventy-two hours after an intravenous injection three to twelve days after an intraperitoneal inoculation, and nine to thirty-six days after an intracranial inoculation.

Eyre described two types of infection in guinea-pigs, the acute and chronic, as follows:

Acute Melitensis Infection.—"Several days after a moderate dose of a highly virulent culture, or a heavy dose of a less virulent culture, the animal dies. For from two to three hours after the injection he

17. Durham, H. E.: J. Path. & Bacteriol. **5**:377, 1899.
18. Carbone, T.: Arch. per le sc. med. **28**:273, 1904.
19. Eyre, J. W. H.: Report Mediterranean Fever Commission, 1905, Part 2, p. 67.

seems to be all right and eats well, but loss of weight sets in, which is highly characteristic for the disease. At first the temperature drops rapidly, then rises. The animal sits huddled up, will not eat, becomes weaker, and if disturbed, goes into tonic convulsions. This stage of increased irritability goes gradually into a stage of coma, from which the animal can be aroused with difficulty, and in which he remains about twenty-four hours with a subnormal temperature. Sometimes he has a convulsion before death, but usually it occurs without warning. The postmortem findings are those of acute septicemia. The organisms can be recovered from all the tissues and organs. In male animals, following intraperitoneal infections, there develops a bilateral purulent process in the tunica vaginalis with beginning hypertrophy of the testes. This pus contains numerous organisms."

Chronic Melitensis Infection.—"With small doses of virulent, or fair doses of moderately virulent organisms, the animal gets a chronic infection. Aside from a progressive loss of weight and a severe anemia, there are no characteristic symptoms. Even the temperature is not much changed. The incubation period of the chronic variety of the disease is from two to three days. Then comes a time, three to six days, when the animal is perceptibly sick. He will not eat, stays in a corner of his cage, loses weight and is very weak. He gradually improves, eats well, even ravenously, and although losing no more weight, he never regains his original weight. Following weeks or months, during which, aside from the loss of weight, the animal seems well, he suddenly dies. Postmortem cultures from the liver are sterile; from the spleen and bone marrow there is sometimes a scanty growth, although these are also often sterile. From the kidneys and the urine a good growth of *B. melitensis* is obtained."

Nicolle and Conseil[20] report on two guinea-pigs which had naturally acquired a *B. melitensis* infection. One animal showed an enlarged spleen. And, again, in their subcutaneous inoculation and feeding experiments they record the findings of a hypertrophic spleen in some of the guinea-pigs examined.

The experiments on which this piece of work is based are divided into two groups. In the first group are included those observations that have a bearing on the relationship of anaphylaxis to cutaneous hypersensitiveness, and of cutaneous hypersensitiveness to immunity and subsequent infection. In the second group are included those experiments that pertain to the pathogenicity of the *B. melitensis* for guinea-pigs, and its relationship to the *B. abortus bovinus.*

---

20. Nicolle, C., and Conseil, E.: Compt. rend. Soc. de biol. **66**:503, 1909; **67**:267, 1909.

In the carrying out of these experiments, that had for their object a study of the relationship of cutaneous hypersensitiveness to anaphylaxis, immunity and infection, the following method was employed. The animals were immunized intensively by the repeated injection of various antigens, the high state of immunity being judged by the agglutination reactions. Intradermal tests were made upon these pigs, the antigen for this purpose being prepared as described in a previous paper. Certain of the animals were then selected for anaphylactic reactions. The proteins used for these tests were prepared, with the exception of the tubercle protein, in which the method described by Austrian[21] was followed, according to the procedure outlined by Zinsser and Parker.[22] After the lapse of a considerable period of time, some of the guinea-pigs were infected with living organisms corresponding to the antigens with which they had been previously immunized, and again cutaneous hypersensitiveness and anaphylaxis were studied.

Those experiments undertaken to determine the pathogenicity of the *B. melitensis* for guinea-pigs, and its relationship to the *B. abortus bovinus,* were carried out as follows: The infecting organisms were injected by the intraperitoneal and intratesticular routes. Twenty-five days after the injection, cutaneous hypersensitiveness was studied, and this was repeated on the fifty-fifth day, using as antigens melitensin, abortin, bronchisepticin and typhoidin. Agglutination tests were made, using the *B. abortus bovinus* and the *B. melitensis* for comparison. The animals were later sacrificed, and careful observations carried out as to gross and microscopic pathology, after the viscera had been cultured to recover, if possible, the invading organisms.

The details of these experiments will not be given at the present time, but will be tabulated carefully and published later.

Careful study of the available data reveals some very interesting facts. By the repeated injection of dead *B. abortus* or abortus protein into guinea-pigs, it is possible to develop a high grade of immunity, as evidenced by the marked agglutinin content of the blood. Incidental to the development of this immunity, these animals became highly sensitized and some of them developed a pronounced anaphylactic state. Cutaneous hypersensitiveness is never present. By subsequently injecting them with living organisms, skin tests are always positive, if on postmortem examinations there is pathologic evidence of infection. Anaphylaxis persists, although its symptoms are neither more nor less pronounced in animals inoculated with dead or living bacteria. That there is an important individual predisposition present in the develop-

21. Austrian, C. R.: Bull. Johns Hopkins Hosp. **24**:141, 1913.
22. Zinsser, H., and Parker, J. T.: J. Exper. M. **26**:411 (Sept.) 1917.

ment of anaphylaxis is proven by the fact that certain guinea-pigs never show symptoms of the anaphylactic state, either after being immunized to or infected with an organism. It is possible to develop an anaphylactic reaction in certain of the guinea-pigs that are injected either intraperitoneally with heat killed typhoid bacilli, intravenously with heat killed typhoid bacilli or intraperitoneally with living typhoid bacilli. In none of these animals is cutaneous hypersensitiveness present. By subsequently injecting these animals with living typhoid bacilli intravenously, either sensitized or unsensitized, the skin tests become positive for a shorter or longer period, the extent of the reaction depending on the dose and the severity of the disease resulting in the guinea-pigs.

It is not within the scope of this paper to theorize on the development of positive skin tests in those animals that are inoculated intravenously with living typhoid bacilli. As far as is known, typhoid bacilli are not pathogenic for guinea-pigs in the sense that they are capable of producing a definite disease with visible anatomical lesions. And again the skin tests were frequently positive when cultural tests failed to reveal the presence of living typhoid bacilli. Whether the hypersensitiveness is a phenomenon depending on the changes elicited in the fixed tissues of the skin or on microscopic foci in the organs following the intravenous injection of living typhoid bacilli, is something that only the future can decide. At any rate, one is justified in stating that it is possible to sensitize guinea-pigs to dead typhoid bacilli and have them highly anaphylactic without the development of cutaneous hypersensitiveness.

The lessons taught by the experiments with the rodent paratyphoid bacillus, which produces in guinea-pigs a distinct disease, characterized by pseudotuberculosis lesions, necroses in the liver and spleen, are much more definite. It is very readily possible to sensitize these animals by the subcutaneous and intraperitoneal injection of heat killed or tricresol killed paratyphoid bacilli without ever developing positive intradermal tests, although certain of these pigs are highly anaphylactic. Subsequently by feeding living organisms, infection takes place as proven by recovery of living bacteria from the feces and postmortem lesions, and the skin tests are invariably positive. The anaphylactic phenomena in animals previously sensitized are neither increased nor diminished following infection.

The importance of the experimental data gathered from the intratesticular injections of *B. melitensis* and the comparison of this organism with the *B. abortus bovinus* can scarcely be overestimated. Serologic and cultural tests previously made by Evans had clearly demonstrated that these bacteria were very closely related. Durham, Car-

bone, Eyre and Nicolle and Conseil had shown that the *B. melitensis* was pathogenic for guinea-pigs, but their descriptions of the pathology of the disease were wholly unsatisfactory. Following the intratesticular injection of certain living *B. melitensis* strains, lesions develop in all of the viscera, which are macroscopically and microscopically absolutely indistinguishable from changes produced in guinea-pigs by the *B. abortus*. Cutaneous hypersensitiveness is positive whether the *B. melitensis* or *B. abortus* is used as an antigen. Likewise if guinea-pigs are infected with abortus bacilli, skin tests are as strongly positive to melitensin as to abortin, although all other bacterial proteins give negative results. The serologic reactions are likewise positive using melitensis antiserum or abortus antiserum with *B. abortus* or *B. melitensis*. It is in this connection, however, in these experimental infections in guinea-pigs that one means is at hand for determining the infecting agent. The serum of animals infected with *B. melitensis* will agglutinate this bacterium in higher dilutions than the *B. abortus*, although the reaction with the latter organism is definitely positive.

These observations logically suggested some experiments on monkeys. As far as a survey of the literature can determine, only Fabyan[23] states that he has injected monkeys with the *B. abortus*, and that he was able to isolate the bacillus from the spleen (?) twelve and thirteen weeks respectively after the infection. The mode of infection, the clinical and serological response to the injected organisms has unfortunately not been stated. Interest naturally centered in discovering whether or not the *B. abortus* produces a temperature reaction similar to the one seen in apes infected with *B. melitensis*. Thus far only the following experiment has been concluded:

EXPERIMENT 1.—Injected macasus rhesus monkey intravenously with 1/10 twenty-four hour slant *B. abortus*, strain 80, April 4, 1919, after he had been under observation for several weeks to be certain that he had a normal temperature. Before injecting, he was bled for agglutination tests, which were negative to *B. abortus* and *B. melitensis*. The animal began to have an irregular temperature on the third day after the inoculation, which persisted up to the time he was chloroformed. On the eighteenth day, agglutination tests were positive with the *B. abortus* in dilution of 1:2,000, *B. melitensis* 1:1,000; on the twenty-fifth day, *B. abortus*, 1:2,000 to 1:4,000, *B. melitensis*, 1:800; on the thirty-fourth day *B. abortus*, 1:600; *B. melitensis*, 1:100; on the fiftieth day *B. abortus*, 1:1,000; *B. melitensis*, 1:600. The animal was sacrificed on the fiftieth day and the spleen, liver, kidneys and mesenteric lymph nodes were found to contain numerous *B. abortus bovinus*. Several skin tests with abortin and melitensin were negative. Microscopically, we failed to find characteristic cellular proliferation.

The infection of this macasus monkey by the intravenous injection of *B. abortus bovinus* is clearly indicated by the febrile course of the disease, the positive agglutination reactions, and the recovery of the

23. Fabyan, M.: J. M. Res. **28**:82, 1913.

offending organism from the viscera postmortem. Further study will be necessary, however, before definite information can be obtained as to the bearing of such a procedure on the possible pathogenicity of the *B. abortus* for man.

CONCLUSIONS

1. Cutaneous hypersensitiveness in guinea-pigs that have been inoculated with *B. tuberculosis, B. abortus bovinus, B. melitensis* or rodent paratyphoid is only positive in the presence of infection.

2. Following intravenous injection of living typhoid bacilli, temporary cutaneous hypersensitiveness can be produced frequently.

3. Guinea-pigs showing a high grade of acquired immunity to an organism, as evidenced by a strongly positive agglutination, complement fixation reactions and complete resistance to a subsequent infection with living organisms, will never give specific positive cutaneous hypersensitiveness.

4. Bacterial proteins, soluble or insoluble, which sensitize a guinea-pig in an anaphylactic sense, will not sensitize its skin. A state of an anaphylactic hypersensitiveness can exist without the least cutaneous hypersensitiveness.

5. The *B. abortus* and *B. melitensis* are very closely related. Guinea-pigs infected by the *B. abortus* give just as strong a skin reaction with melitensin as do guinea-pigs infected with certain strains of *B. melitensis*. From the standpoint of bacterial protein sensitization, the relationship of these two organisms is closer than the one generally recognized between the *B. typhosus* and *B. paratyphosus*.

It is not unlikely that the *B. melitensis* is the caprine strain of the bovine *B. abortus*.

Studies on monkeys, goats and other animals to elucidate this very interesting question are in progress.

PROGRESS IN PEDIATRICS

CURRENT PEDIATRIC LITERATURE

METABOLISM AND NUTRITION

Diabetes in Infancy and Childhood. I. A. Abt.
Endocrinology **3**:273 (July-Sept.) 1919.

Dropsy in Children Due to Fat Starvation. A. B. Grubb.
Virginia M. Monthly **46**:166 (Oct.) 1919.

TUBERCULOSIS AND SYPHILIS

Pleuropulmonary Tuberculosis in Children and Adolescents. L. Ribadeau-Dumas.
Progr. méd. **34**:342 (Aug. 30) 1919.

Tuberculosis in Children. G. H. Cattermole.
Colorado M. J. **16**:244 (Oct.) 1919.

Von Pirquet Test and Results of Its Use. E. Friedman.
Colorado M. J. **16**:246 (Oct.) 1919.

DISEASES OF RESPIRATORY SYSTEM

Asthma in Children. J. Comby.
Arch. de méd d. Enf. **22**:372 (July) 1919.

Bean, Bronchus, in Infant's. Virgilio Craglietto.
Riv. clin. pediat. **17**:477 (Sept.) 1919.

DISEASES OF GASTRO-INTESTINAL SYSTEM

Cirrhosis of Liver in Boy. Pietro Busacchi.
Riv. clin. pediat. **17**:449 (Sept.) 1919.

Indigestion in Children, Chronic Intestinal. G. Fulton.
Kentucky M. J. **17**:400 (Oct.) 1919.

DISEASES OF BLOOD AND CIRCULATORY SYSTEM

Erythrocyte Count at Different Ages. H. I. Bing.
Ugesk. f. Læger **81**:1483 (Sept. 18) 1919.

Heart Action and Nervous Disturbances in Schoolchildren. Alvarez Sierra.
Med. Ibera **8**:94 (Aug. 9) 1919.

Heart Block, Sino-Atrial, in a Child; Effects of Atropin and Vagus Stimulation. N. W. Brown.
Arch. Int. Med. **24**:458 (Oct.) 1919.

DISEASES OF GENITO-URINARY SYSTEM

Bladder, Case of Ectopic Urinary. R. Thompson.
Brit. J. Child. Dis. **16**:80 (June) 1919.

Bladder Stones in Children. E. Suner Ordonez.
Arch. Espan. d. pediat. **3**:449 (Aug.) 1919.

Calculi in Children. R. A. Rivarola.
Semana méd. **26**:18 (July 3) 1919.

Enuresis in Children, Essensial. E. Provinciali.
Pediatria **27**:567 (Sept.) 1919.

Hydronephrosis in Boy of Four. Nicola Iavarone.
Pediatria, **27**:590 (Sept.) 1919.

Phimosis and Disturbance in Micturition in Children. J. A. Phelip and C. de Galard.
Arch. de méd. d. enf. **22**:424 (Aug.) 1919.

Purpuric Nephritis in Children. P. Nobecourt.
Bull. méd. **33**:503 (Sept. 6) 1919.

Urethrocele, Case of Congenital. F. C. Pybus.
Brit. J. Child. Dis. **16**:87 (June) 1919.

DISEASES OF SKIN

Erythema Nodosa and Acute Endocarditis in Boy of Eight. De Meuron.
Arch. de med. d. enf. **22**:428 (Aug.) 1919.

Impetigo Contagiosa in Infancy. J. L. Murray.
Ohio State M. J. **15**:561 (Sept. 1) 1919.

Ringworm Clinic, Experiences at a. H. Davis.
Brit. J. Child. Dis. **16**:93 (June) 1919.

Urticaria and Anti-anaphylaxis. Joltrain.
Arch. de med. d. enf. **22**:481 (Sept.) 1919.

DISEASES OF DUCTLESS GLANDS

Goiter and Iodin, in the School. Weith.
Corr.-Bl. f. schweiz. Aerzte **49**:1474 (Sept. 25) 1919.

Splenectomy, Effect of, on Thymus. F. C. Mann.
Endocrinology **3**:299 (July-Sept.) 1919.

Thymus, Function of. E. Uhlenhuth.
Endocrinology **3**:285 (July-Sept.) 1919.

Thymus; Status Lymphaticus, Case of Enlarged. R. C. Newton.
Am. J. Med. Sc. **158**:534 (Oct.) 1919.

DISEASES OF BONES AND JOINTS

Autovaccine Therapy of Suppurating Skin Diseases in Young Children. Guido Guidi.
Riv. clin. pediat. **17**:393 (Aug.) 1919.

Exostoses, Congenital Cartilaginous. H. Jaeger.
Corr.-Bl. f. schweiz. Aerzte **49**:1461 (Sept. 25) 1919.

Talipes Varus Equinus, Treatment of Congenital. P. Borobio y Diaz.
Arch. espan. d. pediat. **3**:257 (May) 1919.

DISEASES OF EYE, EAR, NOSE AND THROAT

Blindness, Congenital. Joaquin de Salterain.
Rev. méd d. Uruguay **22**:523 (July) 1919.

Blindness with Diabetes Insipidus in Boy of Ten. E. Dameno.
Prensa méd. Argentina **5**:345 (May 20) 1919.

Orbit at Different Ages, Position of Side Walls of Human. J. W. Nordenso.
Acta chir. Scandinav. **52**:45 (May 1) 1919.

Paralysis, Aqueduct of Fallopius and Facial. D. McKenzie.
J. Laryngol., Rhinol. & Otol. **92**:338 (Oct.) 1919.

Tonsillectomy and "Thymus Death." H. Burger.
Nederl. Tijdschr. v. Geneesk. **1**:1951 (May 31) 1919.

Tonsils, Method of Enucleating which Lessens Bleeding. P. MacDonald.
Brit. M. J. **2**:437 (Sept. 27) 1919.

Tonsils, Practical Considerations on Operation for Removal of Adenoids and Enucleation of. W. H. Bowen.
Brit. M. J. **2**:433 (Sept. 27) 1919.

PHARMACOLOGY AND THERAPEUTICS

Laxatives in Infancy and Childhood, Abuse of Catharsis and. L. Fischer.
Med. Rec. **96**:275 (Aug. 16) 1919.

Organotherapy in Certain Diseases and Conditions of Childhood. E. B. McCready.
Med. Rec. **96**:529 (Sept. 27) 1919

Whooping-Cough, Alum in Treatment of. H. P. B. Barfod.
Ugesk. f. Læger **81**:1463 (Sept. 11) 1919.

SURGERY

Tracheotomy as an Emergency Operation. C. Calderon.
Med. Ibera **8**:139 (Aug. 23) 1919.

Tracheotomy without Loss of Blood, Methods of. D. Guthrie.
Surg., Gynec. & Obst. **29**:316 (Sept.) 1919.

MISCELLANEOUS

Babies, Protecting Our Third Line of Defense.—L. Stewart-Cogill and B. M. Meine.
Penn. M. J. **12**:774 (Sept.) 1919.

Backward, Nervous and Delicate Children; Their Treatment and Management. E. B. McCready.
Penn. M. J. **12**:784 (Sept.) 1919.

Children's Diseases. Mercurialle's Pioneer Work in. Aldo Spallicci.
Riv. clin. pediat. **17**:411 (Aug.) 1919.

Dispensary on Basis of Appointments for Patients, Organization of a Children's. E. A. Park.
Mod. Hosp. **13**:185 (Sept.) 1919.

Economic Conditions in the Home, Health and Mind of Children as Dependent on. S. C. Rossi.
Rev. méd d. Uruguay **22**:519 (July) 1919.

Health Status of Runabout Child, Schematic Method for Estimating. C. E. Cater.
California State J. M. **17**:332 (Sept.) 1919.

Hospital, New York Nursery and Child's. M. E. McCormack.
Mod. Hosp. **13**:275 (Oct.) 1919.

Infant Mortality in Uruguay. J. A. Bauza.
Rev. méd. d. Uruguay **22**:489 (July) 1919.

Infant Welfare Work. Ernesto Gaing.
Semana méd **26**:12 (July) 1919.

Infants at Buenos Aires, Welfare Work for. E. Orsi-Battaglini.
Riv. clin. pediat. **17**:460 (Aug.) 1919.

Neustadter Foundation; Convalescent and Recreation Home for Women and Children. York and Sawyer. S. S. Goldwater.
Mod. Hosp. **13**:277 (Oct.) 1919.

Pediatric Problems, Some. H. J. Morgan.
Ohio State M. J. **18**:617 (Oct. 1) 1919.

School, Attitude of Children in. W. Loewenthal.
Corr.-Bl. f. schweiz. Aerzte **49**:1464 (Sept. 25) 1919.

Teeth, Capdepont's Malformation of. P. Fargin-Fayolle.
Paris méd. **9**:200 (Sept. 6) 1919.

Teeth of Schoolchildren. J. L. Johnson.
J. Maine M. A. **10**:38 (Sept.) 1919.

Weaning. E. E. Graham.
Penn. M. J. **12**:716 (Aug.) 1919.

Welfare, Child, a Community Responsibility. W. L. Funkhouser.
J. M. A. Georgia **10**:96 (Sept.) 1919.

Welfare: Protection of Motherhood, Maternity and Child. F. H. Champneys.
J. State Med. **27**:271 (Sept.) 1919.

Welfare Work in France, Child. J. C. Baldwin.
J. M. Soc. New Jersey **16**:310 (Sept.) 1919.

INDEX TO VOLUME 18

PAGE

Acidotic state of normal new-borns, with special reference to alveolar CO_2 tension, alkali tolerance and acetonuria; Max Seham 42
Antineuritic vitamin, rôle of, in artificial feeding of infants; Amy L. Daniels, Albert H. Byfield and Rosemary Loughlin 546
Arthritis, hemophilic, classical case of; May G. Wilson 127
Austin, R. S.: Bacillus tuberculosis in tonsils of children clinically non-tuberculous 14

Birth injuries; review of recent literature on new-born; N. O. Pearce 214
Blackfan, Kenneth D.: Early recognition of hydrocephalus in meningitis .. 525
Blood, chemical examination of, in children; study of 149 cases; Henry Dwight Chapin and Victor Carl Myers 555
Brennemann, Joseph: Incidence and significance of rheumatic nodules in children 179
Byfield, Albert H.: Rôle of antineuritic vitamin in artificial feeding of infants 546

Caloric requirements of normal infants and children from birth to puberty; Fritz B. Talbot 229
Casparis, Horton R.: Cerebral complications in mumps 187
Cerebral complications in mumps; Horton R. Casparis 187
Cerebrospinal fluid, qualitative and quantitative changes in, of various diseases and their significance; A. Levinson 568
Champion, W. M.: Constipating qualities of orange juice 88
Chapin, Henry Dwight: Chemical examination of blood in children; study of 149 cases 555
Child welfare 306
Clothing of infants in summer and winter; L. W. Sauer 20
Convulsions, study of relationship of, in infancy and childhood to epilepsy; John Lovett Morse 73
Courtney, Angelia M.: Fat metabolism of infants and young children; III. Fat in stools of children on mixed diet 107
Courtney, Angelia M.: Fat metabolism of infants and young children; IV. Digestion of some vegetable fats by children on mixed diet 157
Cowie, David Murray: Case of diabetes insipidus in girl of ten years from standpoint of endocrinal involvement 194
Croup, influenzal; Henry Lowndes Lynah 238
Current pediatric literature 69, 149, 224, 312, 522, 591
Cutaneous hypersensitiveness, résumé of some experimental studies on; E. C. Fleischner, K. F. Meyer and E. B. Shaw 577

Daniels, Amy L.: Rôle of antineuritic vitamin in artificial feeding of infants 546
DeBuys, L. R.: Study of stools in children's institutions showing incidence of intestinal parasitic infections 269
Denis, W.: Study of lactose, fat and protein content of women's milk 93
Diabetes insipidus in girl of ten years from standpoint of endocrinal involvement; David Cowie 194
Diphtheria bacilli, new stain for, and consideration of principles involved in staining of this organism; Roy M. Greenthal 25
Dunham, E. C.: Leukocyte counts during influenza in infants and children 153
Dwyer, H. L.: Study of stools in children's institutions showing incidence of intestinal parasitic infections 269

Encephalitis, postinfluenzal; Henry Heiman 83
Epilepsy, study of relationship of convulsions in infancy and childhood to; John Lovett Morse 73

Fales, Helen L.: Fat metabolism of infants and young children; III. Fat in stools of children on mixed diet 107
Fales, Helen L.: Fat metabolism of infants and young children. IV. Digestion of some vegetable fats by children on a mixed diet 157

PAGE

Fat, lactose, and protein content of women's milk; W. Denis and Fritz B. Talbot 93
Fat metabolism of infants and young children; fat in stools of children on mixed diet; L. Emmett Holt, Angelia M. Courtney and Helen L. Fales 107
Fat metabolism of infants and young children; digestion of some vegetable fats by children on mixed diet; L. Emmett Holt, Angelia M. Courtney and Helen L. Fales..... 157
Feces, fat in, of children on mixed diet; L. Emmett Holt, Angelia M. Courtney and Helen L. Fales..... 107
Feces, precipitin reaction in infant stools; Ludvig Hektoen and Clifford G. Grulee 1
Feces, study of, in children's institutions showing incidence of intestinal parasitic infections; L. R. DeBuys and H. L. Dwyer..... 269
Feeding, rôle of antineuritic vitamin in artificial feeding of infants; Amy L. Daniels, Albert H. Byfield and Rosemary Loughlin..... 546
Fleischner, E. C.: Résumé of some experimental studies on cutaneous hypersensitiveness 577
Ford, William W.: Observations on toxic properties of heated and decomposed milk and of milk cultures of *Bacterium welchii* (*Bacillus aerogenes*) 199
Fruits, antiscorbutic property of fruits; experimental study of dried orange juice; Maurice H. Givens and Harry B. McClugage..... 30

Gerstenberger, H. J.: Constipating qualities of orange juice..... 88
Givens, Maurice H.: Antiscorbutic property of fruits; experimental study of dried orange juice..... 30
Greenthal, Roy M.: New stain for diphtheria bacillus and consideration of principles involved in staining..... 25
Grulee, Clifford G.: Precipitin reaction in infant stools..... 1

Health study of boys' school; Richard M. Smith..... 246
Heart disease, congenital; review of recent literature on new-born; N. O. Pearce 298
Heiman, Henry: Postinfluenzal encephalitis..... 83
Hektoen, Ludvig: Precipitin reaction in infant stools..... 1
Hemophilic arthritis, classical cases of; May G. Wilson..... 127
Hemorrhage of new-born; review of recent literature on new-born; N. O. Pearce 207
Holt, L. Emmett: Fat metabolism of infants; III. Fat in stools of children on a mixed diet..... 107
Holt, L. Emmett: Fat metabolism of infants and young children; IV. Digestion of some vegetable fats by children on mixed diet..... 157
Hydrocephalus, early recognition of, in meningitis; Kenneth D. Blackfan.. 525
Hydrocephalus; review of recent literature on new-born; N. O. Pearce.... 219
Hypersensitiveness, cutaneous, résumé of some experimental studies on; E. C. Fleischner, K. F. Meyer and E. B. Shaw..... 577

Infant, new-born, review of recent literature on; N. O. Pearce, 51, 133, 207, 289
Infants, new-born, acidotic state of, with special reference to alveolar CO_2 tension, alkali tolerance and acetonuria; Max Seham..... 42
Influenza, encephalitis following; Henry Heiman..... 83
Influenza, leukocyte counts during, in infants and children; J. C. Montgomery and E. C. Dunham..... 153
Influenzal croup; Henry Lowndes Lynah..... 238
Intestinal flora, certain nutritional disorders of children associated with putrefactive intestinal flora; Langley Porter, G. B. Morris and K. F. Meyer 254
Intestinal parasitic infections, study of stools in children's institutions showing incidence of; L. R. DeBuys and H. L. Dwyer..... 269

Jeans, Philip C.: Cerebrospinal involvement in hereditary syphilis..... 173

Kenyon, Elmer L.: Stammering as disorder of speech dependent on conditions of child development..... 537

Lactose, fat and protein content of women's milk; W. Denis and Fritz B. Talbot 93

PAGE

Leukocyte counts during influenza in infants and children; J. C. Montgomery and E. C. Dunham 153
Levinson, A.: Qualitative and quantitative changes in cerebrospinal fluid of various diseases and their significance 568
Loughlin, Rosemary: Rôle of antineuritic vitamin in artificial feeding of infants 546
Lynah, Henry Lowndes: Influenzal croup 238

McClugage, Harry B.: Antiscorbutic property of fruits; experimental study of dried orange juice 30
McClure, Roy D.: Results of thymus extirpation in dog with review of experimental literature on thymus extirpation 317
Mammary gland, studies on; development of mammary gland from its earliest appearance until period of pregnancy; J. A. Myers 4
Meningitis, cause of "sporadic" case of; Henry L. K. Shaw 101
Meningitis, early recognition of hydrocephalus in; Kenneth D. Blackfan ... 525
Metabolism, fat, of infants and young children; digestion of some vegetable fats by children on mixed diet; L. Emmett Holt, Angelia M. Courtney and Helen L. Fales 157
Metabolism, fat, of infants and young children; fat in stools of children on mixed diet; L. Emmett Holt, Angelia M. Courtney and Helen L. Fales 107
Meyer, K. F.: Certain nutritional disorders of children associated with putrefactive intestinal flora 254
Meyer, K. F.: Résumé of some experimental studies on cutaneous hypersensitiveness 577
Milk, observations on toxic properties of heated and decomposed milk and of milk cultures of *Bacterium welchii* (*Bacillus acrogenes capsulatus*); William W. Ford 199
Milk, study of lactose, fat and protein content of women's milk; W. Denis and Fritz B. Talbot 93
Mongolism; review of recent literature on new-born; N. O. Pearce 146
Montgomery, J. C.: Leukocyte counts during influenza in infants and children 153
Morris, G. B.: Certain nutritional disorders of children associated with putrefactive intestinal flora 254
Morse, John Lovett: Study of relationship of convulsions in infancy and childhood to epilepsy 73
Mumps: See Parotitis.
Myers, J. A.: Studies on mammary gland; development of mammary gland from earliest appearance until period of pregnancy 4
Myers, Victor Carl: Chemical examination of blood in children; study of 149 cases 555

Nutrition, caloric requirements of normal infants and children from birth to puberty; Fritz B. Talbot 229
Nutrition, disorders of, in children associated with putrefactive intestinal flora; Langley Porter, G. B. Morris and K. F. Meyer 254
Nutrition; review of recent literature on new-born; N. O. Pearce 51
Nutritional disorders, certain nutritional disorders of children associated with putrefactive intestinal flora; Langley Porter, G. B. Morris and K. F. Meyer 254

Ophthalmia neonatorum; review of recent literature on new-born; N. O. Pearce 133
Orange juice, constipating qualities of orange juice; H. J. Gerstenberger and W. M. Champion 88
Orange juice, dried, experimental study of; Maurice H. Givens and Harry B. McClugage 30

Parasites, study of stools in children's institutions showing incidence of intestinal parasitic infections; L. R. DeBuys and H. L. Dwyer 269
Park, Edwards A.: Results of thymus extirpation in dog with review of experimental literature on thymus extirpation 317
Parotitis, cerebral complications in; Horton R. Casparis 187
Pearce, N. O.: Review of recent literature on new-born 51, 133, 207, 289
Pediatric literature, current 69, 149, 224, 312, 522, 591

PAGE

Porter, Langley: Certain nutritional disorders of children associated with putrefactive intestinal flora 254
Precipitin reaction in infant stools; Ludvig Hektoen and Clifford G. Grulee 1
Progress in pediatrics 51, 133, 207, 289
Protein, lactose and fat content of women's milk; W. Denis and Fritz B. Talbot 93
Pyloric stenosis in infancy; review of recent literature on new-born; N. O. Pearce 289

Rheumatic nodules in children, incidence and significance of; Joseph Brennemann 179

Sauer, L. W.: Clothing of infants in summer and winter 20
Schoolchildren, health study of boys' school; Richard M. Smith 246
Scurvy, orange juice in; Maurice H. Givens and Harry B. McClugage 30
Seham, Max: Acidotic state of normal new-borns, with special reference to CO_2 tension, alkali tolerance and acetonuria 42
Shaw, E. B.: Résumé of some experimental studies on cutaneous hypersensitiveness 577
Shaw, Henry L. K.: Cause of a "sporadic" case of cerebrospinal meningitis 101
Smith, Richard M.: Health study of boys' school 246
Spina bifida; review of recent literature on new-born; N. O. Pearce 220
Stammering as disorder of speech dependent on conditions of child development; Elmer L. Kenyon 537
Stool: See Feces
Syphilis, hereditary, cerebrospinal involvement in; Philip C. Jeans 173
Syphilis in new-born; review of recent literature on new-born; N. O. Pearce 136

Talbot, Fritz B.: Caloric requirements of normal infants and children from birth to puberty 229
Talbot, Fritz B.: Study of lactose, fat and protein content of women's milk 93
Thymus extirpation, results of, in dog with review of experimental literature on; Edwards A. Park and Roy D. McClure 317
Thymus gland; review of recent literature on new-born; N. O. Pearce 302
Tonsils, bacillus tuberculosis in, of children clinically non-tuberculous; R. S. Austin 14
Tuberculosis bacillus in tonsils of children clinically non-tuberculous; R. S. Austin 14
Tuberculosis; review of recent literature on new-born; N. O. Pearce 221

Vegetable fats, digestion of, by children on mixed diet; L. Emmett Holt, Angelia M. Courtney and Helen L. Fales 157

Wilson, May G.: Classical case of hemophilic arthritis 127

A WORLD GRASP ON MEDICAL LITERATURE

To read all of the worthwhile medical literature of the day is out of the question. To keep one in close touch with the medical thought of the world; to enable one quickly to select just what is related to his special interests; to simplify, systematize and clarify all worthwhile current medical contributions is a service which most reading physicians will at once appreciate. This service is supplied through the

Quarterly Cumulative Index to Current Medical Literature

It enables the user in a minute's time to locate the recent worthwhile contributions to any medical subject. It tells what has been written on that subject; who wrote it; when it appeared; in what publication, and where the publication may be obtained.

It saves time, saves labor and enables even the busiest man to keep tab on the contributions relating to his special problems or interests. To illustrate: A recent issue lists seventy-one articles under the single heading, "Infants." These references are compiled from thirty-six different journals. Twenty of the articles are on "feeding"; ten on "mortality"; eleven on "new-born"; the remainder including the leading articles that have recently appeared on the subject. Eight countries are represented.

Special Features of the Index

Authors and Titles in One Alphabet Oftimes the inquirer knows the name of the author and the subject matter of his article but not the exact title. Sometimes the reverse is true. With the Quarterly Cumulative Index either the name or title is sufficient to locate the article as both are included in the same alphabetical arrangement.

Issued Four Times a Year April, July, October and January. Each new number includes all references in the earlier numbers of the current year; at no time during the year is it necessary to consult more than one alphabet. The fourth or last number for the year is bound in cloth for permanent reference.

A Reliable Index In its preparation the original articles are consulted and reviewed so that the reference will really "refer" not only to the title but also to the subject matter of the article. Every effort is made and no expense is spared to furnish an index of literature and not of titles.

An Index of the World's Literature The original articles in over 200 of the better journals published in the principal countries of the world are listed in this index.

An Up-to-Date Index This index furnishes references to articles published UP TO THE TIME OF GOING TO PRESS.

For permanent reference, the fourth or last number for the year is bound in cloth.

PRICE—$4.00 per current year

AMERICAN MEDICAL ASSOCIATION

535 N. Dearborn St., Chicago, Ill.

— — — — — — — **Sign and Return This Coupon if You Wish to Subscribe** — — — — — — —

SPECIAL ORDER BLANK. American Medical Association, Chicago, Ill.

Gentlemen: Please enter my subscription for the **Quarterly Cumulative Index to Current Medical Literature** for this year (1919) and thereafter unless I order it discontinued. Enclosed please find check for $4.00 for 1919. (Remittance must accompany this order. Foreign postage 50 cents extra.)

Signed..... Address .....

Books from the Press of the American Medical Association

DISTURBANCES OF THE HEART

Second Edition—Revised and Enlarged

OLIVER T. OSBORNE, A.M., M.D.

The newer instrumental methods for the study of the heart, the polygraph, the electrocardiograph, etc., have resulted in a changed conception of the etiology and character of many heart disturbances, and compelled modifications in heart therapy. This book is a discussion of the newer findings from the point of view of the clinician, with special reference to treatment.

Physiologic and drug treatment are covered in a practical manner, and many valuable directions are given as to the management of cases and the regulation of the lives of patients having heart disturbances. Important chapters are those on Heart Disease in Children and During Pregnancy, Cardiovascular Renal Disease, Hypertension, etc. A section is devoted to a discussion of blood pressure. An index affords easy reference to any subject.

Flexible Red Cloth. 269 pp. Pocket size, 4¾ by 7¾ inches. Price, Postpaid, 75 cents

DISTURBANCES OF THE KIDNEY

OLIVER T. OSBORNE, M.D.

New Haven, Conn.

A little 209-page reprint volume written in simple, readable style and with particular reference to the therapeutics of kidney diseases. There are sixteen sections covering anatomy, physiology and function; abnormalities of the urine; albuminuria; renal calculi; hematuria; nephritis; acute nephritis (acute Bright's disease); chronic nephritis; uremia; pathologic condition and anomalies; ureteral catheterization and pyelography; pyelitis; tuberculosis of the kidney; tumors and cysts; the kidneys in pregnancy and disturbances of the bladder.

Silk Cloth. Size, 7¾ by 4¾. 209 pp. Price, Postpaid, 75 cents

SYPHILIS AS A MODERN PROBLEM

WILLIAM ALLEN PUSEY, M.D.

Professor of Dermatology in the University of Illinois, Chicago

This book is a separate reprint in monograph form of the article by William Allen Pusey in the Commemoration Volume issued as a tribute to the medical sciences which made possible the building of the Panama Canal. In this book, Dr. Pusey traces the history of syphilis, calls attention to its symptoms, and discusses the sociologic problems connected with this social disease. The work has been written primarily for the intelligent nonmedical reader, but will be appreciated by physicians.

Pages 129. Price, Postpaid, Paper, 50 cents. Price, Postpaid, Cloth, 75 cents

INFECTION AND IMMUNITY

VICTOR C. VAUGHAN, M.D.

Professor of Bacteriology and Hygiene in the University of Michigan

This book is a reprint in monograph form of the articles by Dr. Vaughan in the Commemoration Volume. It is a direct and reliable presentation of infection and immunity. Sections are devoted to the common infections and the subject is considered primarily from the standpoint of the layman rather than the physician. The latter, however, will find it to be an adequate summary of our modern knowledge of these new subjects.

Cloth. 238 pp. Price, $1.00

NEW AND NONOFFICAL REMEDIES

This is an official publication of the Council on Pharmacy and Chemistry of the American Medical Association. It contains descriptions of those preparations—proprietary and nonproprietary—acceptable to the Council on the date of publication. The description of each preparation includes the chief facts physicians desire to know concerning compositions, dosage, indications, cautions to be observed, etc.

The book also contains the rules of the Council which form the basis of the work.

Every physician who desires to further the cause of scientific prescribing and to aid in diminishing the domination of commercialism in therapeutics in this country should have a copy of this book for ready reference.

Single copy, cloth cover, postpaid, $1.00

THE PROPAGANDA FOR REFORM IN PROPRIETARY MEDICINES

Ninth Edition, Revised and Greatly Enlarged

As New and Nonofficial Remedies covers the field of worthy proprietaries, so the Propaganda for Reform covers the field of the unworthy. Interestingly, even entertainingly written, it contains an enormous amount of information that every physician needs. With New and Nonofficial Remedies and the Propaganda for Reform in his hands, the practitioner can tell what to choose among proprietary remedies—and why; what to avoid—and why. An exhaustive index makes the Propaganda for Reform practically an encyclopedia of unscientific, inefficient and fraudulent proprietaries.

Brown cloth, stamped in gold. 512 pages. Price, Postpaid, $1.00

LAWS

REGULATING THE PRACTICE OF MEDICINE IN THE UNITED STATES AND ELSEWHERE

A New and Completely Revised Edition is issued each year.

This book contains:

(1) Complete information about laws regulating practice in each state of the United States.

(2) A list of foreign medical colleges and brief statements concerning requirements to practice in foreign countries.

(3) Account of latest status of reciprocity in the United States.

From this handbook the physician can learn the essential features regarding practically every law regulating medical licensure and practice. The large sale which this book on laws has received since its first edition is good evidence that it is of inestimable value to the profession.

Paper cover. 230 pp. 5¼ by 8 inches. Price, Postpaid, 50 cents

SUGGESTIONS TO MEDICAL AUTHORS

Including Style Book of the A. M. A. Press and Guide to Bibliographic References.

This pamphlet contains valuable information in regard to the preparation of articles for publication and the points which make an article acceptable.

Paper Cover. 68 pp. Price, 25 Cents. American Medical Association, 535 North Dearborn St., Chicago

THE AMERICAN JOURNAL OF DISEASES OF CHILDREN is published by the American Medical Association as a means for the advancement of the knowledge and for the publication of scientific investigation of the diseases of children.

Manuscripts for publication may be sent to any member of the Editorial Board or to the AMERICAN JOURNAL OF DISEASES OF CHILDREN, 535 North Dearborn Street, Chicago. Books for review, correspondence, communications regarding subscriptions, reprints, etc., should be sent to the latter address.

Articles are accepted for publication on condition that they are contributed solely to the AMERICAN JOURNAL OF DISEASES OF CHILDREN. Manuscripts must be typewritten, preferably double spaced, and the original copy submitted. Zinc etchings, halftones and blocks for colored reproduction of illustrations will be supplied by the publisher when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index published by the American Medical Association. This requires, in the order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. On receipt of stamped addressed envelope, "Bibliographic Style," containing rules for footnotes and bibliographies, and a list of leading medical periodicals of the world, with approved abbreviations, will be sent. "Suggestions to Medical Authors," a comprehensive pamphlet on the preparation of medical manuscripts, which also includes "Bibliographic Style," will be sent on receipt of twenty-five cents.

Matter appearing in the AMERICAN JOURNAL OF DISEASES OF CHILDREN is covered by copyright, but as a general thing, no objection will be made to its reproduction in reputable medical journals, if proper credit is given.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The domestic subscription per year of two volumes is $4.00; Canadian rate, $4.20; foreign rate, $4.35 (18 shillings, 23 francs), including postage. Single copies 40 cents, postpaid.

Make checks, etc., payable to the AMERICAN MEDICAL ASSOCIATION.

CONTENTS

PAGE

THE EARLY RECOGNITION OF HYDROCEPHALUS IN MENINGITIS. KENNETH D. BLACKFAN, BALTIMORE 525

STAMMERING AS A DISORDER OF SPEECH DEPENDENT ON CONDITIONS OF CHILD DEVELOPMENT. ELMER L. KENYON, M.D., CHICAGO 537

THE RÔLE OF THE ANTINEURITIC VITAMIN IN THE ARTIFICIAL FEEDING OF INFANTS. AMY L. DANIELS, PH.D., AND ALBERT H. BYFIELD, M.D., WITH THE COOPERATION OF ROSEMARY LOUGHLIN, M.S., IOWA CITY, IOWA 546

CHEMICAL EXAMINATION OF THE BLOOD IN CHILDREN. A STUDY OF ONE HUNDRED AND FORTY-NINE CASES. HENRY DWIGHT CHAPIN, M.D., AND VICTOR CARL MYERS, PH.D., NEW YORK. 565

QUALITATIVE AND QUANTITATIVE CHANGES IN THE CEREBROSPINAL FLUID OF VARIOUS DISEASES AND THEIR SIGNIFICANCE. A. LEVINSON, CHICAGO 568

A RÉSUMÉ OF SOME EXPERIMENTAL STUDIES ON CUTANEOUS HYPERSENSITIVENESS. E. C. FLEISCHNER, K. F. MEYER AND E. B. SHAW, SAN FRANCISCO 577

CURRENT MEDICAL LITERATURE 591

INDEX TO VOLUME 18 595